A Course of Lectures on Tumors

GIVEN UNDER THE AUSPICES OF THE

CANCER COMMISSION OF HARVARD UNIVERSITY

(Founded by Caroline Brewer Croft, June 16, 1899)

MEDICAL SCHOOL OF HARVARD UNIVERSITY
BOSTON, MASS.
1909

A Course of Lectures on Tumors

GIVEN UNDER THE AUSPICES OF THE

CANCER COMMISSION OF HARVARD UNIVERSITY

(Founded by Caroline Brewer Croft, June 16, 1899)

MEDICAL SCHOOL OF HARVARD UNIVERSITY
BOSTON, MASS.
1909

THE CANCER COMMISSION OF HARVARD UNIVERSITY

(*Founded by Caroline Brewer Croft, June 16, 1899*)

MEDICAL SCHOOL OF HARVARD UNIVERSITY

BOSTON, MASS.

J. COLLINS WARREN, *Chairman.*

HENRY K. OLIVER, J. COLLINS WARREN,
For the Caroline Brewer Croft Fund.

HENRY P. WALCOTT, ARTHUR T. CABOT,
For the Corporation of Harvard College.

WILLIAM T. COUNCILMAN, THEOBALD SMITH,
For the Harvard Medical School.

E. E. TYZZER, *Director.*

ROBERT B. GREENOUGH, *Secretary.*

CONTENTS.

The Bearings of the Experimental Investigation of Tumors on the Tumor Problem in General.*

BY E. E. TYZZER, M.D.,

BOSTON, MASS.,

Assistant Professor of Pathology, Harvard Medical School.

The activity at present shown in the investigation of tumors is amply justified by the importance of this problem to every civilized people. In the case of the infectious diseases there is always the possibility of the development of a considerable degree of racial immunity through the survival of the more resistant individuals. This is shown by the fact that when certain of the infectious diseases are conveyed for the first time to isolated tribes, the latter succumb in far greater numbers than is usual in races accustomed to these diseases. The destruction of certain individuals by malignant tumors, however, fails to produce racial exemption, since such tumors most frequently occur after the reproductive period is past.

The statement of Bashford,[1] that in the deaths of males above thirty-five years of age one in eleven dies of cancer, while in the deaths of females of similar age the ratio is one to eight, indicates the frequency of malignant disease.

The elucidation of the etiology, the early recognition and the cure of tumors constitute the more important goals toward which tumor investigation is directed. The etiology of tumors, for a long time the stumbling block of pathologists, has been a subject for philosophical quite as much as for scientific consideration.

A great variety of methods have, however, been applied to its investigation. The pathological anatomist has made clear the nature of tumors, — that they consist of tissues more or less atypical in structure, but similar to the tissues of the species in which they occur, — that in general they possess powers of unlimited growth, — and that they serve no useful purpose in the organism, but often grow at the latter's expense. Like

* A lecture under the auspices of the Cancer Commission of Harvard University.

[1] Third scientific report of the Imperial Research Fund, 1908.

other tissues, they are composed either of cells, or of cells associated with intercellular substance. It has been found that the rapidly-growing and more malignant tumors are, as a rule, more cellular, whereas many of the slowly-growing tumors possess a large amount of intercellular substance. The number of cell divisions present are also taken as an index of the rate of growth.

The employment of bacteriological methods has resulted in the isolation of various organisms by different investigators. None of the bacteria or yeasts found have been shown to have any causal relation to the development of tumors, and their presence was probably in all instances due either to co-existing infections or to secondary invasion. Subsequent endeavors to discover by the histological study of tumor tissue a causative parasite have resulted in descriptions of protozoa of almost every known as well as of some unfamiliar types. In a former report of the Harvard Cancer Commission, attention was called to the occurrence of similar objects in non-cancerous tissues, and evidence was found strongly indicating that they were not of the nature of parasites. More recently, the presence of spirochetæ in mouse tumors was given, in the absence of any control observations, rather undue importance. I have been able to demonstrate in refractory mice, months after the last inoculation of tumor tissue, large numbers of spirochetes morphologically identical with those occurring in tumor mice. The same organisms were also found in small numbers in uninoculated mice without tumors. As a last resort, cancer is now ascribed by certain adherents of the parasitic theory to an ultramicroscopic organism. It is claimed by Salvin, Moore and Walker that after freezing and grinding mouse tumor tissue with liquid air, a procedure which it is presumed destroys the epithelial cells, the resulting material is still capable of producing tumors on inoculation into other mice. This would amount, then, to the separation of a virus from the tumor tissue, an observation which finds no support in the results of most other investigators who have worked with the inoculable tumors of mice. After the filtration of an emulsion of tumor tissue through ordinary filter paper, the inoculation of the filtrate has been attended with negative results. If the tissue of inoculable tumors is kept at room temperature on its removal from the

body it soon loses its property of producing tumors on inoculation, and this change takes place still more rapidly if incubated at body temperature.

The theories concerning the origin of tumors are so numerous that they will be no more than outlined in this paper. Thiersch and Waldeyer believed that there existed between epithelium and connective tissue an equilibrium, through which the growth of the former was held in check by the latter. On the weakening of the connective tissue in old age, the epithelium is allowed to proliferate, and tumors are formed. Cohnheim attached great importance to displacement of cells or groups of cells from their normal relations during the course of development. The idea of the dislocation of cells was utilized by Ribbert in the explanation of the origin of tumors. He, however, considered other forms of tissue dislocation than that which is represented in the so-called embryonic rests of Cohnheim. He found that epithelial tissue artificially implanted in the connective tissue remained alive for a time and was capable of a certain amount of growth. Epithelial cysts were thus formed, but tissue transplanted in this way possessed only limited powers of growth, and never resulted in a tumor. Ribbert also took into account the loss of the normal relations of tissues in chronic inflammations.

The theory of the gametoid nature of cancer tissue has reached its greatest development with Farmer, Moore and Walker, although it is not original with them. They found that in very early cancers the epithelial cells were penetrated by leucocytes, and from the fusion of these cells of different types a hybrid tissue resulted which possessed the properties of tumor tissue. Further support was found for this theory in the presence in cancer cells of what they considered to be "heterotypical" and "homotypical" forms of mitosis, which had been previously found only in reproductive tissue. In mitotic figures of this sort not only are the number of chromosomes reduced, but the form assumed by the chromosomes is regarded as peculiar to sex cells.

Von Hansemann explains the reduction of the number of chromosomes by means of the intervention of asymmetrical mitotic division. The possibility is suggested that accompanying the loss of chromatin there may be also a loss of differentia-

tion, which he terms "anaplasia." Hansemann does not maintain that anaplasia of itself results in tumor growth. A stimulus is required. He considers it possible that a stimulus which would produce hyperplasia in a normal tissue would produce a tumor when acting on anaplastic tissue. In this connection, the changes found in the chronic pancreatitis in cats, a study of which has been made in this laboratory by Dr. Ordway, are well worthy of attention. The gland cells in certain areas are devoid of zymogen granules, are of small size, and are faintly stained. Mitotic figures are frequently seen, and the activity of this epithelium is evidently formative rather than functional. It would be of interest to determine if this anaplasia of the gland cells is here the result of asymmetrical mitotic division. This sort of gland epithelium is so atypical in its arrangement that structures are produced closely resembling tumor nodules.

Certain principles concerning the regulation of the vegetative and the propagative activities in cells have been discovered by Hertwig and his pupils, but these will be discussed by Dr. Howard in another lecture.

Various facts which have been brought forward tend to show the inadequacy of the theories offered. It is obvious that hypotheses used to bridge over the wide gaps where the facts have not been ascertained add nothing of themselves to the knowledge of the subject. The successful transplantation of epithelial tumors into normal animals of the same species would indicate that a weakening on the part of the connective tissue, as suggested by Thiersch, is not necessary for the growth of tumor epithelium. In fact, the inoculation of tumors is most successful in young animals in which the connective tissue reaction is greatest. With Cohnheim's theory of embryonic rests it is necessary to assume the presence of cells throughout the entire body which have been arrested in the process of differentiation. This, however, does not explain how these cells are stimulated to activity, nor their properties of unlimited growth. The theory of the dislocation of tissues, as advanced by Ribbert to account for the origin of tumors, finds no support in the experimental transplantation of normal tissue, since a true tumor has never been produced in the numerous experiments of this sort, although fetal as well as adult tissues have

been used. That certain tumors grow continuously on transplantation demonstrates a biological difference between tumor cells and the cells of normal tissues.

Apart from the above-mentioned theories, there are certain facts bearing on the etiology of malignant tumors which are coming to be well established. The part played by injuries and chronic inflammation, although repeatedly noted in clinical observation, has been reluctantly accepted by many pathologists. The frequency of the development of carcinoma subsequent to x-ray burns can no longer be ascribed to simple coincidence. The frequency of the development of sarcomata after mechanical injury is now becoming recognized. The development of carcinomata is apparently oftener associated with inflammatory changes of considerable duration. The number of special forms of cancer is continually growing. Bashford, besides mentioning the paraffin, petroleum, arsenic and aniline workers' cancers, the smoker's cancer and the brain cancers of cattle, also describes certain cancers occurring in *unusual* situations and associated with *peculiar* forms of irritation. The so-called Kangri cancer frequently develops upon the abdominal wall of the natives of Kashmir, India, where the custom prevails of maintaining body warmth by means of the Kangri, a small earthenware stove worn suspended against the abdomen.

The " horn core " cancer of cattle occurs where draft animals draw their load by a line attached to the right horn. Tumors are not infrequently associated with parasites. Borrel, Bashford and I have found worms in association with tumors in mice. Cancer of the bladder is frequent in Bilharzia disease, and cancer not infrequently originates in old lupus scars. Attention has been called by numerous investigators to the endemic occurrence of tumors in the lower animals. Whether the prevalence of tumors among animals kept in certain localities or under peculiar conditions is due to the environment in which they are kept or to certain inherited tendencies is not fully proven. The frequency of the occurrence of tumors in such cases scarcely warrants the interpretation of cancer as an infectious disease. It is not improbable, however, that parasites, or even true infections, may have an indirect influence in the origin of tumors.

The work of Loeb on the experimental production of decidual tissue has an important bearing on the origin of tumors. He found that by injuring the endometrium of certain animals, either within a given period after copulation or within a similar period after the phenomenon of heat unattended by copulation, an indefinite number of nodules of decidual tissue could be produced. Growth in this tissue was always simultaneous with the development of corpora lutea, and if the latter were destroyed the decidual tissue then failed to develop.

He concludes that the corpora lutea manufacture a substance which prepares the connective tissue cells of the endometrium for active growth when stimulated later, either by the presence of the ovum or by mechanical injury. That this "preparatory substance" of itself does not produce proliferation is seen by the fact that not all the endometrium in these animals is engaged in the development of decidual tissue. That it affects only the connective tissue of the endometrium and not the connective tissue of the body in general may be due either to the peculiar character of the former or to its association with uterine glands.

It thus seems to be well established that irritations of diverse sorts play an important part in the origin of malignant tumors, but the problem of etiology will not be cleared until it is shown how these conditions excite the tissues to unlimited growth.

Concerning the diagnosis of tumors, much has been done with the end in view of elaborating tests by which the presence of internal tumors could be ascertained. It is well recognized that there are no specific symptoms by which tumors may be diagnosed. In fact, tumors are often far advanced in their development before any disturbance of function is noted. With certain of the experimentally inoculable tumors it has been found that the serum of the animal in which the tumor is growing possessed hemolytic properties for the red blood corpuscles of normal individuals. The corpuscles of the tumor animal are not hemolyzed. Crile has applied this principle in an attempt to obtain a diagnostic test for the presence of tumors. He found that the serum of persons possessing early malignant growths showed marked hemolytic properties, whereas the serum of persons with benign growths did not.

The serum from cases of advanced malignant growths failed to produce hemolysis. The reliability of this test has not been definitely established, although it is not denied that the sera of many cancer cases possess hemolytic properties. Difficulty is found in the fact that the serum in other conditions, notably tertiary syphilis, has been found to be also hemolytic.

For the present, therefore, diagnosis is usually established by the histological examination of excised tissue. Even here difficulties arise. Although in most cases tumors are sufficiently advanced as to make their recognition possible, in certain instances it is impossible to decide whether or not we deal with a tumor. There must be, theoretically at least, all transitions between the normal tissues and tumors. Furthermore, when dealing with recognized tumors it is difficult to decide whether we are dealing with benign or malignant tumors. The nature of the tissue, the relative proportion of cells to intercellular substance, the evidence of invasion of normal tissue and the rate of growth as shown by the frequency of mitotic figures are all taken into account. The distinction between benign and malignant growths, however, remains an arbitrary one, and the possibility of accurately prophesying the future biological behavior of an apparently benign tumor must be questioned.

The subject of treatment will be considered in other lectures of this course, so that I will say nothing more than that the experimental investigation of tumors has shown no mode of treatment which compares with complete surgical extirpation of tumors.

Such are some of the general problems of cancer. If we turn now to the trend of recent tumor investigation, it will be found that there has been great activity in the investigation of experimentally inoculable tumors. The study of the natural incidence of tumors in different species of animals has shown their wide distribution throughout the vertebrate series. Types of tumors are found which are more or less peculiar to certain given species, and tumors appear to be more frequent in some species than in others. Notwithstanding the type peculiarities presented by each species, there is perfect analogy between the tumors of animals and of man. Since in animals we may to a large extent control conditions, opportunity is afforded for the most promising line of investigation. As more study is devoted to the

tumors of any given species, the types of tumors described are constantly increasing in number. Discrepancies in the results obtained by different investigators in this field are usually due to differences in the methods employed. Apolant states that, of the tumors in mice, 95% are external tumors of mammary origin. I have now studied a series of 62 primary tumors in mice, and of these, 37, or about 60%, originated in the lung. The next most frequent type of tumor in my series is the lymphosarcoma, of which there were 10. Only 8 of the 62 tumors were situated externally, and of these, 6 were epithelial tumors. There were 4 tumors of the kidney, 2 of which are undoubted hypernephroma. There were ovarian tumors in 2, and a sarcoma in 1.

Different types of tumors frequently occur in a single animal. Of the 49 animals of this series, 11 presented primary tumors of two types, and 1, primary tumors of four types. In the latter there was a hypernephroma, a lymphosarcoma, a papillary cystadenoma of the lung and an adenocarcinoma of the ovary. About 25% of these cases, therefore, presented multiple tumors of different types. Multiple primary tumors were probably present in a far greater proportion, for in many cases the lung tumors were multiple and occurred not only in single but in several lobes.

Many of the tumors which develop spontaneously in mice and rats have been found to be inoculable. The careful histological study of a series of the inoculated tumors taken at short periods after their injection has shown conclusively that the development of the tumors depends upon the transplantation of tumor cells. The injected tissue is at first surrounded by an exudate which results from the injury caused by the injection. The tumor cells continue to grow, and mitotic figures are found at all stages. There is usually, however, a tendency on the part of the central portion of the implanted mass to undergo necrosis. This necrosis is progressive until the tumor tissue comes to be in actual contact with the connective tissue of the host, and has begun to be vascularized. The stroma of inoculated epithelial tumors apparently undergoes necrosis and a new stroma is furnished by the connective tissue of the host. The reaction of the connective tissue and the blood vessels to the injected tumor tissue varies with different strains of tumors. From this study

it is obvious that production of tumors by the experimental inoculation of tumor tissue is brought about by the transplantation of cells rather than by the introduction of a virus. The tumors, therefore, do not develop from the tissues of the inoculated animal, but from the transplanted tumor cells.

In a former publication[1] I called attention to the frequency of tumors in certain families of mice. In one family of 25 mice there were 4 primary adenocystomata of the lung. Another family was derived by the breeding together of the offspring of a female mouse with a large adenocystoma of the lung. After 100 mice were obtained, the breeding was stopped, and the mice were then kept under observation. Of this family of 100 mice, 89 are now dead. Definite tumors were found in 15 of these. Practically 1 mouse in 6 developed a tumor. A considerable number of these mice died while young of infectious diseases, accidental conditions, etc. Inasmuch as in the above estimate all were counted irrespective of the age attained, the proportion of those developing tumors is large. Thirteen of these mice presented adenocystomata of the lung similar to that which was found in the mother of the family, 2 had mammary tumors in addition to lung tumors, and 1 had double ovarian tumors.

Although the relation of heredity to tumors is studied much more readily in short-lived animals than in man, it is attended with difficulties, especially in the way of providing controls. In this instance another family of mice, which had never developed a tumor, was taken for comparison with the one just mentioned. A tumor of the lung was finally found in a member of the supposedly insusceptible family. It would be necessary, therefore, to show a constant and frequent occurrence of tumors in a given family to establish the existence of an inherited tendency.

Another phase of the study of inheritance was taken up, employing an inoculable tumor. There are numerous observations on racial differences of susceptibility to the inoculable tumors. The attempt has not to my knowledge been made of carrying out systematic breeding experiments for the determination of the part played by heredity. The tumor used in this case originated in a Japanese waltzing mouse, and proved

[1] Fourth report of the Cancer Commission of Harvard University, 1907

to be peculiarly adapted for this sort of experimentation. From the first it grew in practically 100% of all waltzing mice inoculated. Its rate of growth was slow, but fairly uniform, and tumors which attained large size showed but little necrosis, so that inoculations were attended with uniform results.

The attempt was made to inoculate common, tame mice with this tumor with negative result. The idea then suggested itself of obtaining hybrids and determining if they were susceptible. Hybrids were obtained by breeding together common males and Japanese waltzing female mice. Such hybrids were found to be susceptible, and the tumors grew more rapidly in them than in the control waltzing mice. Hybrids were obtained from Japanese waltzing males and common females. These were also susceptible. These results suggested that the susceptibility to the inoculable tumor might be of the nature of a Mendelian character, which would then necessarily be dominant since it was apparent in the first generation of offspring. The Mendelian expectancy would be, therefore, that in the next generation 25% of the mice would be insusceptible.

Fifty-four mice of the second generation of hybrids were inoculated, with negative result in every case. In two or three of this number the tumor tissue evidently grew for a time, but later became rapidly absorbed in every case. These results indicate clearly that the susceptibility to this inoculable tumor is not to be considered an inherited character of the Mendelian sort.

Sixteen mice of the third generation of hybrids were inoculated in order to determine if the susceptibility might reappear. These proved, however, also insusceptible.

From these data it is evident that heredity is of considerable importance in the interpretation of results in the investigation of the inoculable tumors. Its influence is seen in the great susceptibility of Japanese waltzing mice, and in the absolute insusceptibility of common mice. There is, however, no evidence of Mendelian inheritance of susceptibility or insusceptibility, so that the influence of heredity remains obscure. These results are of biological interest in that the tumor grows in certain varieties of mice and fails to grow in others, although the different varieties breed freely with each other.

In order to determine the nature of the insusceptibility of the

second and third generations of hybrids, a histological study is now being made of the subject. The tumor has been taken at different intervals of time after its inoculation into comparative series of susceptible and insusceptible mice. Japanese waltzing mice were used for susceptible and second-generation hybrids for insusceptible stock. The reaction of the host tissue to the inoculated tumor was practically identical in susceptible and insusceptible mice up to the seventh day. The tumor epithelium had acquired a stroma and had become largely vascularized in the insusceptible as well as in the susceptible mice. The next preparations taken at ten days, however, showed a complete and apparently sudden necrosis of the tumor epithelium, while in the susceptible mouse there was a well-established tumor. This result indicates the development of an immunity subsequent to the inoculation.

Curative properties have been claimed for the serum of mice refractory to tumor inoculation. Large doses of defibrinated blood of previously inoculated insusceptible hybrid mice were inoculated into mice with tumors. In the small number of cases done no curative action was observed.

In testing the susceptibility of the various series of mice, observations have been made concerning the effect of the growth of the tumor on the rest of the body. In a series of mice which developed tumors of great size there was distinct hypertrophy of the heart, and the weight of the body apart from the tumor was increased as compared with controls. The liver was in some instances several times the weight of the normal, but this was probably in part due to congestion through failure of compensation. The kidneys and spleen were also increased in weight. The enlargement of the spleen, however, probably resulted from the absorption of toxic substances from the necrotic portion of the tumor. It seems that this increase in the weight of the organs represents a hypertrophy brought about by the extra weight and possibly the nutritional demands of the tumor.

An attempt was made to find some relation between the rate of body growth and tumor growth. It was found, however, that there was no constant correlation. In some instances the most rapidly growing animals, while in others the slowly growing animals, produced the largest tumors. In their ultimate

development, tumors attain greater size in large than in small animals. It seems probable that the nutrition of the body is sufficient for a time for the needs of the tumor as well as for the developing tissues. It appears that in some instances the demands of the tumor tissue are greater than those of the normal tissues. In one instance five young mice which had been inoculated all presented tumors.

One mouse, which was rather smaller than the others, lost weight and finally became emaciated. The tumor developed in this mouse, but was much smaller than in any of the others. It was found that this mouse had been gradually starved through a deformity of the teeth, preventing its eating. The rate of tumor growth had been diminished by the starvation, but it nevertheless grew to a certain extent at the expense of the rest of the body.

The pessimism sometimes expressed concerning the cancer problem serves only to discourage investigation. It is evidently based in many instances on the assumption that all tumors arise from congenital defects or abnormalities. The successive description and exploitation of a long list of pseudo-parasites have served to bring discredit to this field of investigation, and the inadequacy of various theories advanced concerning the origin of tumors has served to strengthen the doubt. It is sometimes stated that there is no advance in our knowledge of tumors. In addition to the establishment by clinical observation of the part played by chronic inflammation, the experimental investigation of tumors has yielded certain definite results, which show such statements to be erroneous.

First it is proven by transplantation experiments that cancer cells differ biologically by their property of unlimited growth from normal tissue cells.

Peculiar conditions are not essential for the continuation of this growth. Certain tumors grow in normal individuals. Other tumors, however, require a special soil; they grow if transplanted into other parts of the same individual, but not if transplanted to other individuals.

Growth is found to depend upon the biological character of the cells and not upon their dislocation.

The experimental investigations have made untenable the interpretation of cancer as an infectious disease.

The development of sarcoma in animals inoculated with epithelial tumors is interpreted by most investigators with whom it has occurred to be the result of the irritating influence of the tumor epithelium.

The demonstration of the presence of substances which prepare tissue for growth on subsequent injury or stimulation is of great importance.

There is, therefore, no more basis for pessimism with regard to the tumor problem than there was formerly for a similar attitude with respect to the problem of the infectious diseases. The latter remained unsolved until the advent of the experimental method of research. The experimental investigation of tumors has been but recently taken up, and it has already yielded valuable results. The problems of growth are of broad biological significance, and they should not be considered solely from the point of view of medicine. Up to the present time no more is known of the principles regulating normal growth than is known of those principles concerned in the abnormal growth of tumor tissue. It is possible that the investigation of one may eventually throw light on the other. The essential problem is, therefore, one of growth, and its investigation concerns the biologist, the zoölogist and the embryologist, as well as the physician.

The Histological Classification of Tumors.*†

BY F. B. MALLORY, M.D.,

BOSTON, MASS.,

Associate Professor of Pathology, Harvard Medical School.

Normal cells and tissues are classified according to striking morphological characters which distinguish different kinds of cells from one another. These characters, aside from size and shape of cells and nucleus, may lie within the cell (eosinophilic granules, axis cylinder processes) or be extracellular substances produced by the cells (collagen fibrils, osteoid substance). They represent the differentiation which the cells undergo in order to perform their different functions.

Tumor cells tend to differentiate like normal cells; hence tumors are usually classified histologically like normal tissues, that is, according to the microscopic structure of their cells and intercellular substances. In tumors which grow slowly, the differentiation of the cells is usually well marked; in those which grow rapidly, it may be slight or wanting. It is important, therefore, to study embryological as well as normal tissues so as to have a clear knowledge of how muscle and other cells look in the early stages of differentiation. A knowledge of embryology is also useful in explaining the location of certain tumors (a glioma over the coccyx) and the nature of such a tumor as the chordoma which arises from remains of the notochord, a fetal tissue.

In classifying tumors, it is important to ascertain what is the one essential cell in each type of simple tumor and to name the tumor accordingly, leaving out of consideration the blood vessels and connective tissue of the stroma. They are furnished by the tissues in the midst of which the tumor develops because there is a physiological demand made for them by the tumor cells. All tumors composed of one type of cell, at whatever

* A lecture under the auspices of the Cancer Commission of Harvard University.

† Synopsis of lecture, which was illustrated by one hundred and twenty-seven lantern slides.

rate of speed they are multiplying, should be considered under one heading, not separated into slowly and rapidly growing groups and described separately. Such a separation is artificial and misleading.

The essentials for the exact diagnosis of tumors, especially those which are growing rapidly, are perfectly fresh tissues obtained at the operating table if possible, immediate fixation in proper solutions which will preserve faithfully all the morphological characters on which an exact diagnosis depends, and special staining methods to render prominent the characteristic structures.

A limited number of characteristic cells will be described and some varieties of tumors composed of them will be demonstrated photomicrographically.

The ordinary connective tissue cell or fibroblast is an elongated, flattened cell with a flat, oval nucleus. It is characterized by the production of two kinds of fibrils (fibroglia and collagen fibrils) which can be stained in sharp contrast to each other. The fibroglia fibrils are in intimate contact with the cytoplasm of the cell; the collagen fibrils are entirely free from it; they both run parallel with the long axis of the cell. Cells of this type produce a series of tumors ranging from the dense fibroma to the soft rapidly growing fibrosarcoma (so-called spindle-cell sarcoma). Even in the most rapidly growing tumors of this series both kinds of fibrils are produced, although they may be very delicate and few in number. Occasionally some of the cells contain multiple mitoses and others large lobulated or multiple nuclei with numerous centrosomes.

The myxoma andm yxosarcoma differ from the tumors of this group only in having a certain amount of fluid, containing more or less mucin, between the collagen fibrils. They should not, therefore, be classed as a separate type of tumor.

The smooth muscle cell is a long spindle-shaped cell with a rod-shaped nucleus. It is characterized by a number of fine striations running longitudinally in the cuticle of its cytoplasm. Towards the tapering ends of the cell these striations, termed myoglia fibrils, coalesce more or less intimately to form what appear to be coarse fibrils. Slowly and rapidly growing tumors composed of this type of cell (leiomyomata) occur most commonly in the uterus, but may arise in other parts of the body.

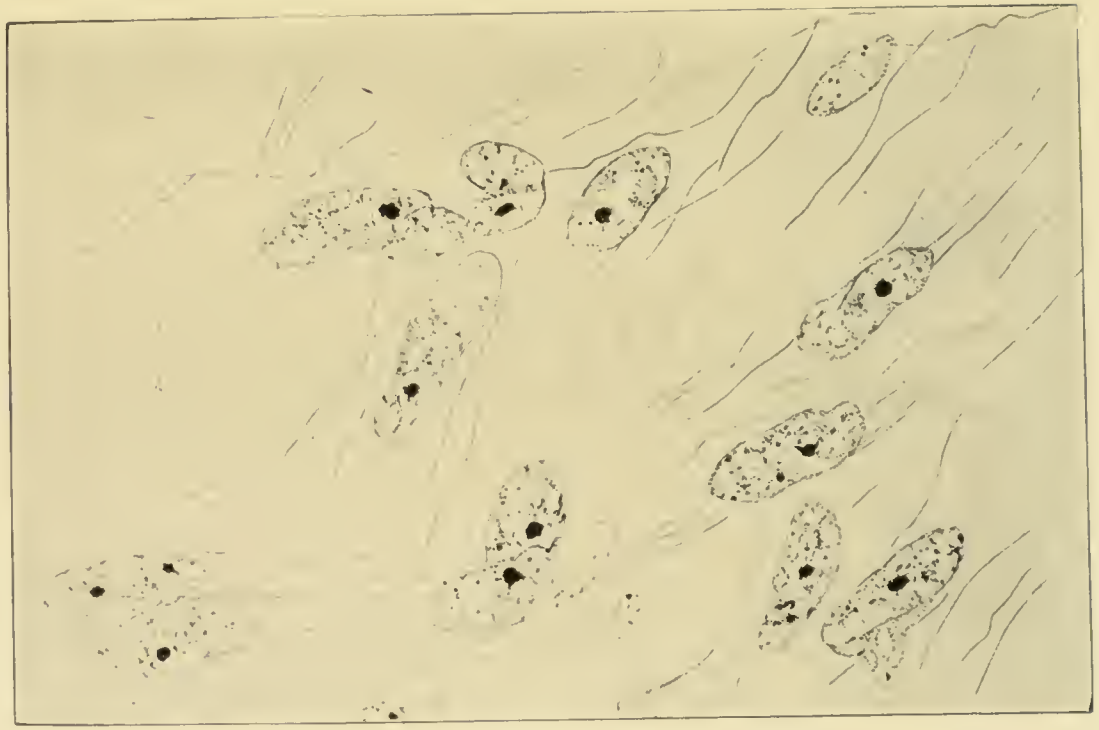

FIG. 1.

Fibrosarcoma: cells viewed flat-wise: fibroglia fibrils black: collagen fibrils barely visible.

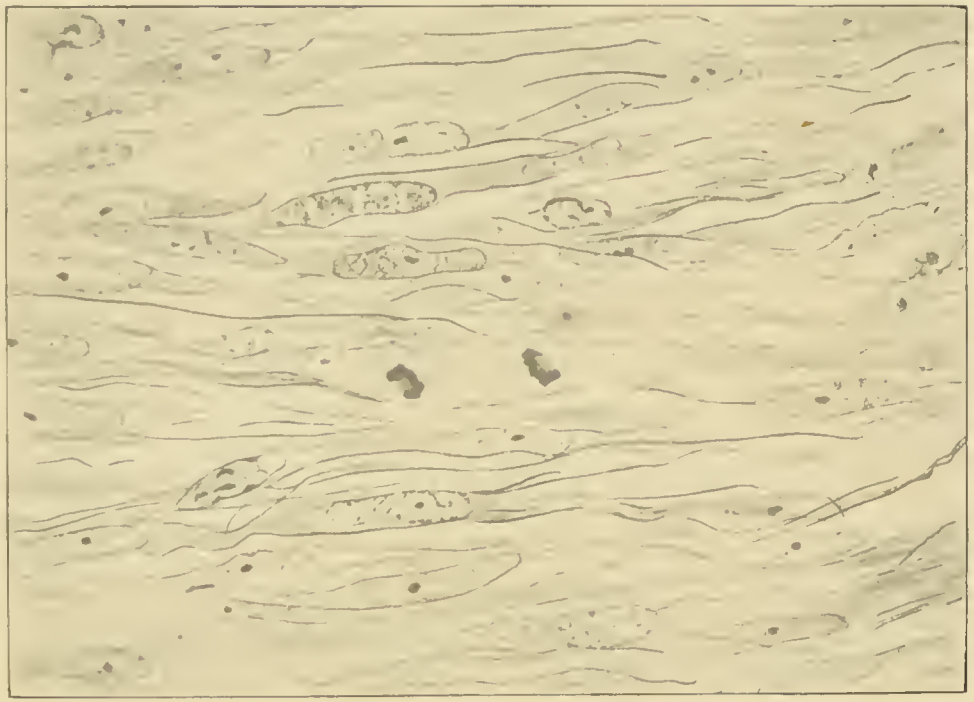

FIG. 2.

Malignant leiomyoma: one cell in mitosis, numerous myoglia fibrils present

FIG. 3.

Glioma: numerous neuroglia fibrils surround the cells and run in all directions.

In one rapidly growing malignant leiomyoma, in parts where the cells were proliferating most rapidly, they ceased forming fibrils and became more or less spherical in shape.

The neuroglia cell varies considerably in shape and size. It may be round or spindle shaped, or of intermediate form. It is characterized by the production of fibrils of one kind only, the neuroglia fibrils, which run parallel with the spindle-shaped cell and in all directions around the spherical cells. These fibrils touch the cytoplasm of the cell to which they belong in some part of their course. From this type of cell quite a variety of gliomata arise, some of which grow slowly, while others multiply rapidly and may invade the pia of brain or cord and grow along it. One glioma occurring over the coccyx and giving rise to metastases in both groins evidently arose from remains of the neural canal.

The endothelial cell is characterized by no production of fibrils; hence it stands out in marked contrast to the cells already described. It gives rise to two types of tumors, the hemangio-endothelioma and the lymphangio-endothelioma. The first type occurs in two varieties, the capillary and the cavernous.

The capillary hemangio-endothelioma occur in the form of small blood vessels which invade fat, muscle and nerve tissues, and occasionally grow within veins and arteries. The endothelial cells sometimes form several layers around the lumina of the vessels, giving the appearance of a perithelial growth, and rarely papillary masses of endothelial cells may project into the lumen of a vessel and more or less occlude it. If through rupture or pressure the lumina of the vessels become obliterated, the endothelial cells grow in masses and whorls. After a time collagen fibrils extend in between the endothelial cells from the connective tissue cells of the stroma and transform the tumor into what looks like a fibrosarcoma, but fibroglia fibrils are lacking.

In four cases of gradually extending cavernous hemangio-endothelioma the tumors were found to consist of endothelial cells, supported by thin layers of connective cells and fibrils, growing within and along blood vessels. In places they distend or burst through the vessel walls so as to form tumor nodules composed of large blood spaces separated by thin septa of connective tissue covered on both sides with endothelial cells.

A neuroma of adrenal origin, with widely distributed metastases, was characterized by masses of delicate fibrils which reacted to a variety of stains like nerve fibrils.

The neuromata of the eye have been shown by Verhoeff to consist of nerve cells which tend to differentiate like the cells of the retina. The rosettes occurring in these tumors often show very definite rods and cones projecting through an external limiting membrane just as the normal rods and cones do.

In the rhabdomyoma the cells tend, by differentiation of the cytoplasm, to produce the sarcous elements of the normal fetal striated muscle cells.

In the chordoma occurring at the base of the skull the curious vacuolated cells of the notochord are faithfully reproduced.

Epithelial cells occur in great variety; so, also, do the epithelial tumors of which the cells tend to differentiate like the normal cells. It is advisable, therefore, to study by themselves each type of normal epithelial cell and the group of tumors with cells differentiating like it. Only the names of a few can be mentioned here: The adenomata of the mammary and coil glands with the layer of smooth muscle cells surrounding the epithelial cells; the various types of carcinoma of the breast; the characteristic benign and malignant epithelial tumors of adrenal cell origin; the chorio-epithelioma derived from fetal epithelium covering the chorionic villi; the ciliated epithelial tumors derived from remains of the Wolffian duct, and the adamantinoma derived from remains of the enamel organ.

The vague terms "spindle and round-cell sarcoma" and "perithelial angiosarcoma" should be avoided so far as possible. A spindle-cell sarcoma may be composed of connective tissue, smooth muscle, endothelial or neuroglia cells. A round-cell sarcoma may in reality be a lymphoma, osteosarcoma, malignant leiomyoma or neuroma. A true perithelial angiosarcoma does not occur. The tumors which most frequently show such an appearance are the melanotic sarcoma and the neuroma of the eye; rarely even a carcinoma of the breast may exhibit this type of growth which is purely nutritional in origin. The cells at a distance from the blood vessels undergo necrosis and absorption, leaving the vessels isolated with a sheath of tumor cells around them.

Some Aspects of the Pathological Physiology of Intracranial Tumors.*

BY HARVEY CUSHING, M.D.,

BALTIMORE, MD.,

Associate Professor of Surgery, Johns Hopkins University.

INTRACRANIAL growths are of peculiar gravity to the individual inasmuch as they affect the most vital organ of his body. To the physiologist and pathologist they are of peculiar interest by reason of the light they often shed on the localization of function and the unusual physical disturbances which arise in consequence of their origin within a rigid bony chamber. To the clinician they are of peculiar importance owing to their frequent occurrence and the ease with which they may be overlooked.

There seems to be little basis for the prevalent belief that a brain tumor is a relatively rare lesion, particularly if we are to include with " tumors " the infectious granulomata, cysts and the neoplasms which arise in the cerebral envelopes and subsequently crowd their way into the cranial cavity. Oppenheim goes so far as to regard the brain as the seat of predilection for new growths, and Bruns with some severity affirms that when a general practitioner says he has never encountered an instance of this disease, it is an acknowledgment that cases have passed through his hands unrecognized. Unquestionably failure to appreciate the existence of intracranial growths in the early stages is among the commonest of diagnostic errors.

Nor is it difficult to advance a reason for this state of things. In reviewing the possible causes of a given train of symptoms one naturally inclines toward the malady for which the greatest relief may be expected from established methods of treatment. For this reason syphilis is apt to be thought of first in the case of brain tumors. The early recognition of any disease of insidious onset is apt to go hand in hand with successful therapeutic

* A lecture under the auspices of the Cancer Commission of Harvard University, Feb. 25, 1909.

measures; if these are vague, uncertain, unavailing, interest becomes lax and the disease reaches a full-blown stage, which fits the textbook description considered typical of the malady, before the patient attracts any earnest attention and is induced to enter the wards of a general hospital. Hence the opportunity for observing any large number of cases of intracranial tumor in their incipiency is unusual, and, owing to the comparative infrequency of prompt surgical exploration in the suspected cases, there has been little chance of gaining a first-hand knowledge of the early lesion, of acquiring familiarity with the associated pressure phenomena and of studying the absolutely fresh tissue. Furthermore, it has been unusual likewise for these unfortunates to end their days in the wards of an active hospital, for most of them have a pitifully long history and frequently gravitate to asylums for the mentally afflicted, where an unsuspected tumor is often disclosed at autopsy, as Blackburn's figures from the Government Hospital for the Insane indicate. But even if the story has terminated in a general hospital, a post-mortem view of the terminal stages of tumors of the brain, as of other organs, naturally gives the impression of operative impossibility, which largely accounts for the hopeless outlook that statisticians have held in regard to these lesions. . .

Since the opening of the Johns Hopkins Hospital, twenty years ago, the pathological records show that, up to Jan. 1, 1909, in 3,150 autopsies, there were 55 cases in which brain tumor was found, — about 1.7%, or 1 case in 57 autopsies. This is an even larger percentage than that given by Seidel, who found, in Munich, an average of 1 case in 80 autopsies, or 1.25%; and by v. Beck, who found, in Heidelberg, an average of 1 case in 120 autopsies, or 0.8%. There are, of course, many elements to be considered in these figures, such as the average age of hospital patients, the character of the hospital service, the interest paid to neurological cases, etc.

Bruns states that .2% of all patients classified as "neurological" suffer from brain tumor, and Blackburn's figures (29 tumors in 1,642 autopsies, nearly 3%) show an equal percentage for all mentally afflicted (i. e., asylum) patients.

In the medical wards of the Johns Hopkins Hospital, in approximately 25,000 admissions up to Jan. 1, 1909, there have been in the neighborhood of 20 cases diagnosed as brain tumor (?) in each succes-

sive 5,000 admissions, making an average of 1 tumor case in every 250 patients.

In Dr. Halsted's surgical service, since the opening of the hospital in 1889, the number of patients with the diagnosis of brain tumor has risen from .06% in the first 5,000 admissions to 0.2% in the second 5,000; to .3% in the third 5,000; to 0.75% in the fourth 5,000; to 1.3% in the last 3,000 (i. e., from Jan. 1, 1907, to Jan. 1, 1909). In the last 1,000 surgical admissions there have been, up to the present date, 40 brain tumor cases, showing the rapid increase in the percentage of these patients in a general service to 4 in every 100 admissions.

The disturbances occasioned by a tumor have been conveniently divided into (1) *general pressure symptoms*, which in a measure occur irrespective of the situation or histological character of the growth; and (2) *focal or localizing symptoms*, which are manifestations that indicate the area of the brain implicated. For example, the familiar benign endothelioma which arises from the meninges in the cerebello-pontine angle, in the course of its enlargement and encroachment on the intracranial space, will ultimately produce headache, vertigo and paroxysmal vomiting, together with the well-known alterations in the eye-grounds, and at the same time will definitely call attention to its situation by evidences of involvement of the adjoining cerebellar hemisphere, as well as by pressure palsies in the distribution of the cerebral nerves which emerge from the pons in its immediate neighborhood.

This commonplace illustration of the fully developed symptomatology applies to the condition ultimately to be expected in the course of most cases of tumor when the diagnosis is written on the patient's retina if not on his face. What will soon be demanded of us will be the recognition of such a lesion before its symptoms are thus outspoken — no easy matter, for we are cut off from the more familiar methods of a physical examination bequeathed to us by Auenbrugger and Laënnec, and only the distant effects of a brain tumor, not the actual lesion, are accessible to the eyes, ears and fingers.[1]

[1] It is true that inspection is indirectly aided by the ophthalmoscope and occasionally by the x-ray; palpation, by the chance thinning of the bone overlying a growth. Percussion, likewise, is at times useful, as Phelps and Macewen have pointed out, and auscultation similarly may detect an aneurismal bruit. But these are exceptional rather than usual opportunities.

I. THE GENERAL EFFECTS OF TUMORS.

In the first place, a tumor may give rise to pressure symptoms alone when it occupies a " silent " or " mute " area of the brain, and in consequence of our scant knowledge of the function of the larger part of the cerebrum the majority of such tumors remain absolutely unlocalizable, even if their presence be suspected. On the other hand, a brain tumor early in its development may give local symptoms alone, with no appreciable pressure phenomena, should it have originated in a " speaking " in contradistinction to a mute or silent area; in other words, when it primarily implicates centers or paths the function of which is well understood. Finally, a brain tumor may be present for years and give rise to none of the symptoms considered characteristic of a new growth, so that a diagnosis of dementia, hysteria, psychoneurosis, migraine, headache from eyestrain, dyspepsia or nephritis, and what not, is made in the attempt to explain the symptomatic disturbances which may be present. A tabulation of the various diagnoses made in the early stages of a series of brain tumor cases would make a professionally disconcerting record.

One of Hughlings Jackson's characteristic dicta reads, " The study of the thing caused must precede the study of the cause of the thing," a consoling epigram, for with certain of the symptomatic pressure phenomena of brain tumor we are still in the stage of " studying the thing caused," and this is notably true of the headache and vomiting — symptoms which do not readily lend themselves to experimental methods of investigation.

It is quite probable, in the case of the headaches at least, that the " cause of the thing " in all instances is pressure. Here, however, we are confronted with a problem very similar to that which has puzzled physiologists and surgeons in the case of abdominal pain. The organ itself, the brain, — like the liver, the spleen and the intestines, — is insensitive, as is also its immediately investing membrane. The cranial cavity, however, is lined with and partitioned by an outer sentient membrane, the dura, whose sensory fibers, trigeminal and vagal, are capable of demonstration by dissection. It has been observed that patients, after removal of the Gasserian ganglion or

severance of the trigeminal nerve, no longer suffer from the sensation of headache on the anesthetic side of the head.[1] These facts would favor the view that the dura plays a part at least in these subjective discomforts; but it has been found in a number of instances in which cranial operations have been performed without anesthesia upon conscious patients that the dura is actually insensitive to touch or incision, and that a sensation of pain is elicited only when traction is made upon it. This condition is again comparable with that found in the case of the abdominal viscera, and Meltzer's view, that it is the mere exposure of the viscera in an enfeebled patient that leads to their apparent insensitiveness, is difficult to reconcile with what we know of other definitely sentient tissues. It would seem, therefore, that distortion of the falx or tentorium and the consequent dragging upon or stretching of the membrane may be an important factor. We know, for example, that headaches are often particularly agonizing in cases in which the dural pocket enclosing the hypophysis cerebri is distended by an enlargement of the gland, and that they cease as soon as the capsule has been incised. It has been learned, furthermore, that the headaches of tumor are often promptly and completely relieved by a successful " decompressive " operation, and even when a certain amount of discomfort persists after these measures, its severity varies with the degree of tension evident in the protruding area. Indeed, many headaches not associated with tumor may be of pressure origin. This is certainly true of the headaches of traumatic edema and of nephritis, and may be so even of ordinary migraine, judging from certain operative experiences which we have met with in these cases.[2]

As the German proverb tells us, " Where there is much light, the shadow is deeper." And it must be admitted that there are many points in relation to headache not entirely explained by assigning pressure as the cause. Thus, a lumbar puncture with withdrawal of cerebrospinal fluid from a healthy individual, which supposedly brings about a lessening of the normal degree of tension, may occasion great intracranial discomfort,

[1] The Sensory Distribution of the Fifth Cranial Nerve. Johns Hopkins Hosp. Bull., 1904, vol. xv, p. 223.

[2] A subtemporal decompression, performed in an intractable case of this sort upon a physician who had suffered for years from hemicrania, afforded an unexpected degree of relief.

and there are definite reflex headaches of gastric or ocular origin, and possibly those of anemia, which are difficult to reconcile with this view. Moreover, problems arise whose solution is for the psychologist rather than the physiologist. Perception of pain is unquestionably a cerebral function, for without the brain it is inconceivable that it should exist, and yet the brain itself (with the possible exception of the basal ganglia), so far as we know, is insensitive to the stimuli which give pain at the periphery. Faradization of the supposed sensory cortex in two conscious patients, though giving vague tactual impressions referred to the periphery, was provocative of no local sensation whatsoever.[1]

Particularly vague is our knowledge of the agencies which provoke the so-called cerebral vomiting — a symptom inconspicuous or entirely wanting in two thirds of the cases, even after they have reached an advanced stage when other evidences of pressure are pronounced. Whether there is a center for this act in the medulla — possibly vagal — can only be conjectured, but the symptom is thought to be more common when the bulb is involved. I have seen a case in which occasional projectile vomiting persisted for months after the successful removal of a frontal lobe tumor, in spite of the disappearance of all other signs of pressure.

In the case of choked disk, however, our views are clearer, for it is an objective process and lends itself readily to experimental study. Time forbids a relation of the development of our knowledge of this interesting lesion — the most important of all symptomatic evidences of intracranical pressure, for the discovery of which we are indebted to Helmholtz and his "optical toy," as he was wont to call the now invaluable ophthalmoscope. Of the many views advanced in explanation of the process, a number have been based on conjecture alone, but of the two most important, one would ascribe the lesion to purely mechanical or pressure agencies, the other to purely toxic or inflammatory factors.[2]

---

[1] A Note upon the Faradization of the Post-Central Convolutions of the Human Brain in Conscious Patients. Brain, 1909, vol. xxxii.

[2] Hence a terminology has arisen which is confusing. "Optic neuritis" or "papillitis," introduced by Von Leber and signifying inflammation, as opposed to "choked disk" (Clifford Albutt's adaptation of the German term, "*Stauungsoedema*") or "papilledema," suggesting the swelling of vascular stasis, are variously used by different

Numerous observations, experimental and clinical, have served in the past few years to turn the scale in favor of the mechanical origin of the lesion. Thus, a condition typical of the early stages of choked disk has been found to accompany the non-inflammatory traumatic edemas described by Cannon and Bullard, which so often follow fractures of the skull; again, the close affinity between the neuroretinal lesion of tumor and of nephritis has been demonstrated; further, it has been shown experimentally that a choked disk may be produced by increasing the intracranial pressure through the introduction of fluids or of a sterile elastic foreign body within the skull. But most conclusive of all is the rapid subsidence of the process which often follows the release from pressure brought about by the establishment of an adequate cranial and dural opening.

After Schwalbe's discovery that the investing sheath of the optic nerve was merely a prolongation of the meninges, its compartments communicating with the intracranial (subdural and subarachnoid) spaces, it became known, through the experiments of Schmidt-Rimpler, Manz and others, that an acute distention of the optic sheath comparable to the ampullaform dilatation, well known to pathologists in cases of brain tumor, will occur if fluid under pressure is allowed to enter the intermeningeal spaces enveloping the encephalon. These observations have been confirmed by others as well as by workers in the Hunterian laboratory,[1] where it has been shown that the distention of the optic sheaths, with accompanying congestion and edematous swelling of the nerve-head,— a choked disk in its early stage,— will occur not only in consequence of the introduction of fluid maintained under increased tension, but that the fluid normally present in the cysternæ about the infundibu-

writers to express the whole process or to indicate its different stages. It would seem desirable to fix upon one term to describe the lesion from its early to its terminal stage; that is, from the early vascular congestion of the nerve-head and retina, through the stage of marked swelling of the papilla with exudates and hemorrhage, to the final stage of new tissue formation, atrophy and blindness. For this entire process, personally I should prefer to reserve the term " choked disk " rather than to limit this designation to a stage of the lesion in which there is a certain measurable degree of swelling. Marcus Gunn has suggested the term " tumor papillitis," which is undesirable, for the process seems to be the same whether produced by the edema accompanying cerebral injuries, vascular disturbances, nephritis or tumor; and " papillitis " suggests inflammation as the primary element — a view that more recent opinion has not supported.

[1] Observations on Experimentally Induced Choked Disk. Johns Hopkins Hosp. Bull., 1909, vol. xx, p. 95.

lum may play the same part in case an increase of intracranial pressure is similarly maintained by the introduction into the cranium of bodies simulating tumors. The fluid seems to pass, for the most part, into the subarachnoid spaces of the optic sheath, though in certain instances it may distend the subdural space as well. It has not been finally determined whether the fluid finds its way from the distended sheath into the neuro-retinal tissue by lymphatic channels or whether the swelling which occurs is the result of a stasis in the central veins brought about by the greater tension of the fluid encompassing the nerve. Probably both elements play a part; but, however this may be, a rapid edema does occur, and if by proper devices the pressure can be maintained for days or weeks, the edema, as elsewhere in the body when accompanied by venous stasis, is followed by extravasations and infiltration, which in the course of time through the process of new tissue formation will shut down on the nerve and lead to atrophy and blindness.[1]

There are other " things caused " by general pressure which need no more than mention in passing. Among these are vertigo and dizziness, convulsions, the medullary symptoms with slowing of the pulse and a transient rise in blood pressure (usually a terminal and much less striking phenomenon than in the cases of acute compression due to sudden vascular lesions), and finally,— what Dr. Bordley and I have come to regard as an early manifestation of tumor,— the inversion or interlacing of the color fields. This symptom has been definitely wanting in only two of a series of forty cases in which a careful perimetric examination was possible, and thus promises to be a fairly constant feature of pressure from tumor, wherever its location, and irrespective of the presence or absence of an accompanying choked disk. This must be regarded as an important matter in view of the supposed relation of this phenomenon to hysteria. Moreover, this is one of the first symptoms to disappear after a decompression, so that the normal relations of blue, red and green often return long before the complete subsidence of an accompanying choked disk (Figs. 1 and 2). Failure to investigate the eyegrounds and plot the visual fields in the physical

[1] By certain writers a process similar to that which occurs in the optic nerve has been described for the acousticus (" choked labyrinth " or " *Stauungslabyrinthe* "), but the clinical demonstration of the effects of such a process is inconclusive, and it has received no sufficient pathological or experimental confirmation.

examination of a patient the victim of headaches is equivalent to a neglected urinalysis when there is pain in the back and edema of the feet.

We must turn from these symptomatic manifestations of the lesion to see, if possible, what has been taking place within the skull. The primary effect of most tumors is an encroachment on the space which normally should be completely occupied by the brain and its vascular and cerebrospinal fluids — the *Raumbëengung* effect of the Germans. I say "most tumors," for there are certain diffuse gliomatous growths which infiltrate and destroy the nervous tissue as they advance, and pressure phenomena may be absent unless a sudden hemorrhage or edema leads to an abrupt onset of these symptoms, with the clinical picture of apoplexy or thrombosis. Indeed, not only those of pressure, but all other signs may fail if such a lesion originates in a silent field, or if, as often happens, the growth prove to be a glioma which is traversed by intact nerve fibers.

The usual consequence, however, of the gradual encroachment by the new foreign body on the cerebral space is a crowding away of the neighboring brain substance, which suffers more through compression than from actual invasion of the tissue. The effects of this process are felt locally more than at a distance, especially since there is a certain degree of partitioning of the cranial chamber, so that the pressure is more or less discontinuous, owing to the presence of the dural septa. The hindbrain, for example, is particularly well protected by its suspended dural roof against pressure exerted from above, and this is especially true in certain of the lower animals who possess an ossified tentorium. A slowly-growing tumor in a favorable situation may often attain a large size, the gradual pressure causing excavation with atrophy of the neighboring cerebral substance out of which the tissue fluids have been slowly but permanently expressed — for it must be remembered that the cerebral tissue itself is practically incompressible — without seriously jeopardizing the functions of the remoter portions.

As a rule, however, the pressure effects of a growth are transmitted in some degree throughout the entire intracranial chamber. This occurs in a number of ways: through circulatory stasis, through the intermediation of the cerebrospinal

fluid in one way or another, and through dislocation and change of position of the cerebral or cerebellar hemispheres.

Circulatory stasis is naturally one of the earliest results of pressure, for the slightest increase affects primarily the outflow from the veins, whose fluid tension is normally very low. External evidences of this stasis are not only observable in the eyegrounds, but are also shown by a fullness of the extracranial vessels of the scalp and eyelids, whose content normally passes in large part through the intracranial sinuses on its way to the heart. The distention in some cases may be extreme.

Now, the cerebrospinal fluid, which is constantly being secreted by the ependymal cells lining the choroid plexuses in considerable quantities — the amount being possibly increased under conditions of venous stasis — normally escapes from the skull in large part, if not wholly, through the intermediation of the arachnoidal villi which project into the sinuses and their dural expansions. Hence interference with the escape of this fluid may occur in consequence either of some obstruction to the free passage of blood through the sinuses — for it has been shown experimentally that these are compressible channels — or of an occlusion of the arachnoidal villi, possibly by the small herniæ of cerebral substance which Wolbach has demonstrated to be an accompaniment of marked degrees of pressure.

In all cases in which pressure phenomena are present and the obstructed fluid has acquired an increased degree of tension, it collects and distends the basilar cysternæ, finding its way into the optic sheath; hence the choked disk. It also passes into the olfactory nerves; hence its occasional escape from the nares (rhinorrhea); and into the spinal canal, where it may be demonstrated under increased tension if one wishes to take the risk of performing a lumbar puncture in these cases. But back of this a still more important complication may arise from this stasis of the cerebrospinal fluid, in case the lesion is so situated as to obstruct the outflow of fluid from the ventricles by compression of the iter or one of its foramina of outlet from the ventricles. A ventricular distention from this source is almost inevitable at some stage in the progress of subtentorial lesions, though it is by no means confined to them, for the iter or one or both foramina of Monro may become obstructed by cerebral growths or even by those arising from the pituitary body. The

complication, as would be expected, always serves to greatly exaggerate pressure phenomena, which are often absent until it occurs. It is possible that the obstructive hydrops of the ventricles may lead to certain recognizable symptoms referable to the hypophysis itself, a portion of whose secretion (as Herring has shown, and as we also have found) normally passes directly into the infundibular prolongation of the third ventricle. But this we will touch upon in a later paragraph.

And this brings us to the question of cerebral dislocation, an important matter, inasmuch as failure to appreciate its significance may lead to errors of localization and treatment, and since on the principle of its occurrence much of our present surgical therapy hinges.

For the purpose of studying the dislocation effects of tumors, it is essential that the brain be hardened *in situ* before its removal (preferably by carotid injections of formalin into the carotid) even at the sacrifice of the best methods of fixing the tissues for finer histological study. Furthermore, when possible, it should be removed with its meningeal covering intact. One can depend upon the macroscopic study of a brain prepared only in this way for an accurate appreciation of the topographical relations of the growth, with the accompanying dislocation of the meningeal septa, the degree of ventricular hydrops and the extent of the foraminal herniation.

This last condition deserves a word of especial emphasis, for it is not only a frequent cause of sudden death, but illustrates at the same time the principle upon which palliative operations are founded. Particularly in the presence of a lesion of the hind-brain with secondary hydrocephalus, though the same thing is true also of a growth above the tentorium whose pressure effects are far reaching, the nervous tissues tend to become molded or herniated into any defect in the investing meninges. At the foramen magnum is a natural defect, and, in consequence, the bulb, with a surrounding fringe of cerebellum, crowds its way through this opening in the effort to escape from the pressure within the chamber.

It is for this reason that the sudden withdrawal of fluid from below by a lumbar puncture may lead to serious bulbar symptoms from the local anemia thus produced by a further wedging of the medulla within the foraminal ring. The same thing takes

place, of course, when there is a sudden increase of pressure from above through edema or hemorrhage into a growth, and it is well known that these bulbar symptoms are the usual terminal event in most cases of brain tumor.[1]

An embarrassed, possibly rhythmic, respiration is the first evidence of the medullary compression, an excess of which may suffice to completely stop spontaneous respiratory activity. Under these circumstances artificial aids to breathing may tide over the first few perilous moments, and a consequent rise in blood pressure may reawaken the activity of the anemic centers. But in some cases spontaneous respiration is never resumed and the heart continues to beat as an isolated organ so long as the artificial aids to the act are continued. On one occasion during the past winter this accident occurred before recovery from the anesthetic in a patient subjected to lumbar puncture during the course of an operation, and after artificial respiration had been continued for twenty-eight hours the cranium was widely opened by a large osteoplastic resection and the brain examined. It was gray in color, absolutely without circulation, and, though after its exposure some of the larger arteries were seen to fill and pulsate, there was no through-and-through circulation. Stimulation of the exposed motor field by a powerful faradic current failed to elicit any movements whatsoever on the contralateral side of the body. On another occasion artificial respiration with a tracheal canula and bellows was continued for a period of three days, and it is conceivable that the cardiac action might have been continued for a week had it not been finally stopped by an attempted revival with adrenalin — death of the central nervous system beyond resuscitation having doubtless occurred soon after the circulation was shut off from the medulla.[2]

---

[1] An analogous disturbance in the case of the pontine centers may follow the postoperative dislocation downward of the mid-brain when a suboccipital exploration has been made in the case of a lesion which, lying in or above the pons, proves to be inaccessible.

[2] It is possible that patients in this condition, with a paralyzed respiratory center, might be revived by a prompt suboccipital exposure of the foraminal region. Since writing the paragraphs above, the measure has been successfully carried out in a patient with tumor suffering from sudden respiratory failure, though not from a lumbar puncture. Artificial respiration was promply instituted and continued for forty-five minutes while the imprisoned cerebellar margin was exposed and liberated. There was an immediate resumption of spontaneous breathing, and recovery followed. A cerebellar cyst was found and evacuated at a later sitting.

On this same principle there is a tendency for the cortex to protrude through and to enlarge any openings, even minute ones, and in this way are produced the small herniæ which have been described by Wolbach as occurring at the situation of the arachnoidal villi. These herniæ sometimes assume considerable proportions and become as large as peas, and, if Pacchionian granulations in adult life have already formed at the situation of the villi, they may even lead to complete absorption of the immediately adjacent parts of the cranium.

Enlargement of the head due to separation of the sutures, with the peculiar change in the cranial percussion note, is a well-recognized symptom of tumor, particularly when in young individuals obstructive hydrocephalus has occurred; and the widening of the skull affords marked, often unexpected, relief from the pre-existing pressure symptoms. This diastasis of the sutures, however, can only be looked for in cases of long-continued and excessive pressure, in which, some time before the bones have separated, the choked disk has gone on to its atrophic stage; hence it is unusual to find vision present even in very young children whom nature has relieved in this way. An equally effective natural method of relief may result from the local pressure absorption of the skull should a growth lie immediately subjacent to it. We have seen a number of instances of this — chiefly in temporal lobe tumors — in which the thinned squamous wing of the temporal bone has been absorbed so that the mass forms a protrusion under the temporal muscle very similar to that which occurs as a result of the palliative operation which has been devised with this particular object in view. The dislocation outward, or the hernia of the brain which occurs after the making of such a purposeful defect, need not, to accomplish its object, occur directly over the situation of a tumor, and, indeed, there are certain objections to thus placing it, for a sudden dislocation of this kind has been shown to lead not infrequently to large extravasations within the substance of the underlying vascular growth, owing to the very change of position which was the object of the operation; for this change of position can easily be seen to favor the rupture of the delicate, thin-walled vessels which feed many tumors.

II. THE LOCAL EFFECTS OF TUMORS.

Though not entirely inappropriate to the scope of this lecture, a discussion of the neurological disturbances, functional, paralytic and irritative, consequent upon lesions in various parts of the brain would lead us too far afield. There are certain points, however, which deserve to be noted. Localization of function in the cerebrum is a concept of our own time, and that we are still forced to allude to " mute areas of the brain " is no occasion for reproach when the intricate difficulties of the problem are appreciated. Accessions to our knowledge of the structure and function of the nervous system follow one another more rapidly than is the case with any other organ or system of organs in the body. The combined labors of many lead to this end,— investigations into the finer anatomy of the nerve cells, into the study of nerve tracts as they become primarily myelinized or secondarily degenerate, into the effects of excitation of different areas or of experimental lesions in the animals nearest man. Thus the recent work of Horsley and his co-workers on the accurate subcortical placement of experimental lesions leads us to hope for great advancement in our knowledge of function of the heretofore inaccessible basal ganglia; and the studies of Bolk and Van Rynberk promise to give us a knowledge of localization of function in the cerebellum comparable to that which we now possess for the cerebrum.

Man differs from the lower animals chiefly in the greater development of his central nervous system, and profitable as the studies of cerebral function in the lower animals have been in the past and will doubtless always be, the rapid advancement in our knowledge in the sensory field can only be made by the study of the effects of purposeful lesions on man, for he alone is able to communicate an interpretation of his sensations. Such experiments, of course, are out of the question, and our observations must necessarily be confined to the detailed investigation of such symptoms as arise in the course of disease, in the expectation that post-mortem examinations may reveal a sufficiently circumscribed lesion to make the condition comparable to that of a physiological experiment. This, however, is rarely the case, for by the time death occurs, the lesion, particularly if it be a tumor, will have rendered the degenerated

pathways so obscure as to make their study unprofitable. To be sure, the situation of certain lesions giving a peculiar symptomatology was first made out in this way by the incomparable studies of Broca and of Hughlings Jackson, and much may still be expected from a similar correlation of gross pathological findings with clinical symptoms. How large a part surgery is to play in the furtherance of our knowledge in these regards will depend upon the preliminary training in neurology and neurological pathology of those who are to undertake this kind of work. Their privilege in this respect must be regarded as a liability rather than an asset, for to accept the opportunity of advancing knowledge is no light responsibility.

This point is well illustrated by the case of the hypophysis cerebri, — the so-called brain gland, — an organ until within recent times regarded as a functionless tissue relic which, according to our predecessors, discharged pituita or mucus into the nose. It is the frequent seat of enlargement and of tumors which give a definite intracranial symptom-complex, owing largely to the immediate juxtaposition of the optic chiasm. Physiologists had shown that an extract of the posterior lobe of the gland contains a blood-pressure-raising principle (Howell) and causes diuresis (Schäfer and Herring) and here the matter rested until the observations by Paulesco — which have been corroborated in the Hunterian Laboratory — brought out the surprising fact that surgical removal of this physiologically active posterior lobe does not appreciably affect the individual; whereas, on the other hand, removal of the entire gland, or of the anterior lobe alone, leads, usually in the course of a few days, to a fatal issue with a peculiar train of symptoms. Hence the pituitary body is a structure as vital to the maintenance of life as are the parathyroid bodies or adrenal glands.

Clinical studies, furthermore, have suggested some intimate relation between hypophyseal activity and that not only of other ductless glands (the thyroid, thymus, ovary, etc.), but of various other functions. Thus it is connected in some way with the process of growth observed in dwarfism, gigantism and acromegaly, the activity of the generative organs (amenorrhea and sexual infantilism), the deposition of fat (adiposis dolorosa and Fröhlich's disease) and possibly other conditions. Marie's belief that the acromegaly is due to a primary hypo-

physeal lesion has not been uniformly accepted, and those who agreed with him doubted whether it was the result of a hyper- or a hypo-secretion of the gland, a matter which a single surgical observation has served to conclusively determine. Thus Hochenegg removed a portion of the enlarged gland from a woman suffering from acromegaly, and, as a result, not only did the local pressure symptoms disappear and menstruation return, but there also took place a rapid shrinkage of the previously hypertrophied tissues of the hands, feet and face. An equally striking result has followed a partial hypophysectomy in a case of my own.

As has been intimated in the earlier paragraphs, it is possible that in almost all tumor cases the hypophysis suffers to a certain degree, and one might expect its function to be particularly interfered with when there is an obstructive hydrocephalus, for Herring has shown that the posterior lobe of the gland discharges its secretion directly into the infundibular cavity of the third ventricle. From a clinical standpoint it is suggestive that amenorrhea is a not infrequent accompaniment, often an early symptom, of brain tumor in women, and further, that after removal of the growth, or even after simple decompression, the menstrual function may be resumed. Another suggestive clinical fact is the rapid accession of weight which is often seen after these operations — more than can be accounted for by the withdrawal of drugs, the improved appetite and cessation of vomiting. One of our patients who had a cerebellar tumor accompanied by a low grade of hydrocephalus gained fifty pounds in the sixteen weeks following the extirpation of the growth. One is tempted to speculate upon a possible connection between this improvement and a restored activity of the pituitary body, and it may be added that our autopsies have invariably shown not only some histological alteration, but more or less structural deformation of the hypophysis, particularly marked when there was some obstructive dilatation of the third ventricle.

There are certain things, however, more strictly pertaining to the local effects of tumors which I wish to dwell upon. One of them concerns the relation of a growth to the surrounding structures. It is well known that a lesion which originates, for example, in the bone, the dura or from the cerebral nerves,

will be slow to invade the encephalon itself, however deeply it may become molded from pressure, owing to the barrier offered by the delicate leptomeninges; also that the enucleation of such a lesion leads to prompt restoration of function. On the other hand, when symptoms such as hemiplegia, hemianopsia or aphasia are occasioned by a new growth which has originated in the brain substance itself, it is widely believed that they will inevitably be perpetuated if the lesion be extirpated; in other words, that the symptoms are the result of an anatomical destruction rather than a physiological " block " of the pathway involved. If the centers themselves, ganglionic or cortical, have not been destroyed by pressure-anemia or tumor invasion, the degree of restoration of function is often astonishing and shows not only that pressure disturbances are much more common than destructive ones, but also that the power of restoration of function is surprisingly great. In a patient with total hemiplegia and hemi-anesthesia, after a subcortical sarcomatous cyst the size of a tennis ball had been removed intact, there ensued almost complete restoration of the contralateral motor and sensory paralysis in the course of two or three weeks. We have also seen a complete restoration of previously hemianopic vision in cases in which the sight had been affected simply from pressure upon the optic pathway. The recuperative powers of the brain, even when large areas of tissue have been removed with a tumor, are often extraordinary; and as our ability to localize tumors improves, they will be approached at an earlier stage and there will be less likelihood of damage, whether from invasion, long-continued compression or surgical injury. The old view that lesions limited to the paracentral convolutions which called early attention to their presence by the motor irritation or paralysis were alone suitable for surgical attack is rapidly being superseded.

The difficulties of making a local diagnosis of a lesion advance rapidly with the appearance of general pressure symptoms, supposed by many to be essential for the making of a diagnosis at all. It will be long, I fear, before physicians will awake to this fact. In many ways the general pressure phenomena rapidly obscure the main issue, and through distant edemas through dislocations, through ventricular hydrops and what not, secondary or indirect symptoms (*Fernsymptome*) are pro-

duced which greatly confuse the primary focal manifestations. Then, too, the patient's mental processes invariably become affected in some degree, and when blindness has ensued, the difficulties may be still further increased. In illustration may be mentioned the case of a small boy in whom, owing to headaches, a tumor had long been suspected, but no careful neurological study had been made until his failing vision had gone on to blindness. At this stage he was first thoroughly examined, with an operation in view, and the only focal symptoms were suggestive of a lesion of the left cerebellar hemisphere, which on two occasions was thoroughly exposed and examined. He subsequently died, two years after the first onset of symptoms, and an operable benign tumor, such as would unquestionably have produced an homonymous hemianopsia as its earliest symptom, was disclosed at autopsy in the left occipital lobe. The growth had slightly dislocated the tentorium downward and occasioned the left cerebellar symptoms. Many other illustrations of this sort might be given.

One may say, therefore, that the more pronounced the general pressure symptoms — the phenomena characteristic of tumor — the less the likelihood of making the focal diagnosis which is essential to the success of the only curative therapeutic measure,— removal of the lesion.

III. THE HISTOLOGICAL PATHOLOGY OF TUMORS.

And now, after these general words as to *what the tumor does* and *where the tumor lies*, remains the final and, possibly, in view of the foundation upon which this lecture is given, the more interesting question of *what the tumor is*. On this matter, unhappily, I feel far less competent to speak.

Needless to say, except in the case of evident metastases from a malignant growth elsewhere [1] and of the occasional undoubted syphiloma or solitary tubercle, in which the history is clear or concomitant foci of disease are recognized, a pathological diagnosis before the lesion can be seen and handled is difficult in the extreme, even though certain growths have

[1] Of these I have encountered six during the past year,— a melanotic sarcoma from an unrecognized primary melanoma of the ovary, a cystic sarcoma secondary to a growth in the neck, and four instances of carcinoma occurring some years after a radical operation for cancer of the breast.

certain seats of predilection. Indeed, it is often difficult to tell whether the general and local symptoms are, after all, actually due to a new growth, for they may be closely simulated by a formidable array of lesions; by vascular disease — thrombosis, embolism, aneurism, even apoplexy; by the edemas of nephritis, which may give characteristically focal symptoms; by certain chronic inflammations such as those of the ependyma, which may occlude some foramen of outlet for the cerebrospinal fluid; and lastly, by certain post-traumatic cysts. Furthermore, there is a group of cases — the so-called pseudo-tumors of Nonne — in which careful post-mortem studies have revealed no lesion whatsoever, though the ante-mortem symptoms, general and focal, were definitely characteristic of tumor.

But the difficulties do not end with the clinical diagnosis; they follow us to the laboratory, where the dissimilarity of the growths, even those which from a cytological standpoint evidently belong in the same group, makes a satisfactory terminology often troublesome, sometimes impossible. One important thing has been pointed out by Dr. F. B. Mallory, and that is the necessity, for satisfactory microscopical studies, of the immediate fixation of absolutely fresh tissue; and such material in the case of brain tumors — indeed, in many others — can only come through the intermediation of surgery. Dr. Adolph Meyer, too, has strongly emphasized the need of making sections of the entire tumor, for in the same growth areas of widely different histological character are to be seen.

When one considers the difficulties of satisfactorily classifying, for example, the various epithelial tumors of the mammary gland,— tumors which in a fresh state, in large numbers and in all stages, are available for histological study,— it is easily comprehended how much greater are the difficulties in the case of the brain, where an unusual variety of neoplasms are to be found, epithelial growths arising from the hypophysis or choroidal ependyma, congenital tumors, the meningeal endotheliomata, cystic formations of peculiar and varied sorts, to mention but a few of the lesions besides those which are specific of the central nervous system,— the gliomata.

These very gliomata by no means invariably conform to the accepted description either of their gross or finer anatomy. They need not, for example, infiltrate the brain, for we have

encountered many examples in our series of about one hundred cases in which on all sides they were as definitely demarcated as the endothelial growths which affect the brain by compression rather than invasion. Gliomata seem to have an especial predisposition to cystic degeneration, and it would seem that the entire growth may at times become completely transformed into a cyst. Instances of this have been noted by Sir Victor Horsley, and elsewhere some personal experiences of the same kind have been recorded.[1] Thus on one occasion a large inoperable cerebellar tumor, presumably a glioma, was exposed by a suboccipital operation. Death occurred some six months later, and the autopsy disclosed a cavity the size of a goose's egg surrounded by a thin shell of cerebellum and filled with a semi-fluid, grumous, broken-down, brownish tissue mass, no tumor cells whatever being found on histological examination of the surrounding walls.

Such an occurrence in the history of a cerebral growth is presumably due to the shutting off of the local vascular supply, with death of the entire tumor mass; and it may be said that the centers of many of the larger gliomata show, in like fashion, a tendency toward gelatinous or cystic metamorphosis. A process of this kind seems to occur more frequently in gliomata of the hemispheres, cerebral or cerebellar, than in those arising from the basal ganglia, possibly as the former may attain a larger size and their vascularization become less secure. As usually encountered, the cysts contain clear fluid which often clots but otherwise resembles cerebrospinal fluid. It seems to be secreted in considerable amounts, so that there is a tendency for the cysts to refill even after their evacuation. Studies of the cyst wall not infrequently show in certain areas a persisting zone of new growth, and the cavity is usually lined with a delicate, loosely-attached membrane. Whether this represents a secreting membrane, or whether the fluid is merely lymph from the adjoining nerve-tissue which discharges into the cyst, can only be conjectured, especially since little is known of the lymph-flow in the tissues of brain and spinal cord. Cerebrospinal fluid, as is well known, will not be taken up and absorbed for any length of time by the areolar tissue. This has been well

[1] Removal of a Subcortical Cystic Tumor without Anesthesia. Jour. Am. Med. Asso., 1908, vol. I, p. 855.

shown by the futile attempts to effect its discharge into the loose subaponeurotic layer of the scalp in cases of hydrocephalus. For some days the scalp remains edematous, but soon the fluid becomes confined in a definite pocket, which acquires a smooth endothelial lining.

To further the progress of surgical therapy a more accurate knowledge of the lymphatics of the brain and their relation to the cerebrospinal fluid circulation is, as pointed out in a previous section, one of the present needs in our study of the brain tumor question, and the function of the much-neglected choroid plexus probably represents the key to the situation. Were it not for occasional difficulties on this score, our present-day operative methods would give almost total relief to the pressure phenomena and would permit, in cases of tumors occupying silent areas, either of subsequent enlargement sufficient to call attention to their situation, or would allow time for degeneration in the cases in which this favorable outcome occurs.

During the past year Dr. G. J. Heuer and I have been given the privilege by the pathological department of the hospital of making first-hand studies of all of the brain tumor cases which come to autopsy, and thus we have gained the invaluable experience of making our own gross and histological examination of tissues and of comparing the findings with the results of our previous neurological examinations. Only in this way can errors of diagnosis and faults of surgical therapy be intelligently correlated. In the matter of histology, we have received the kind co-operation of Dr. Mallory, and it is our hope that with his aid we may be able at some future time to speak more in detail in regard to this feature of the work. Up to the present time our attention has been largely confined, as the title of this lecture indicates, to the functional disturbances from tumors occurring in various regions of the brain, regardless of their anatomical makeup.

In conclusion, I wish to recall briefly some points touched upon in this lecture that possibly deserve this additional emphasis.

Contrary to the common belief, brain tumors are of frequent occurrence, and possibly there is no disease in which the symptoms are more often overlooked or incorrectly interpreted. For the sake of successful palliative or curative measures, a

precocious diagnosis is necessary, and a careful clinical study of all suspected cases at an early stage, with a more intimate knowledge of the local and general pressure phenomena, will tend toward this desired goal.

A more widespread familiarity with the early appearance of the neuroretinal edema and congestion is needed, and also the understanding that this condition is merely a stage in the process of choked disk. Inversion or interlacing of the boundaries of the color fields, heretofore regarded as pathognomonic of hysteria, has been found to be a fairly constant early phenomenon in tumors.

One recognized characteristic of the brain under pressure is its tendency to herniate through a cranial defect, and as there is normally an opening at the foramen magnum, a certain degree of protrusion is usually present there. In the presence of such a condition, the withdrawal of the cerebrospinal fluid from the spinal meninges by a lumbar puncture is often hazardous, as it may tend to a sudden wedging of the bulb in the opening, with anemia and paralysis of the vital centers.

The pituitary body proves to be one of the most important of the ductless glands. It not only may be the primary seat of a new growth, but in the case of intracranial tumors elsewhere, particularly when they are accompanied by hydrocephalus, its function may secondarily become disturbed in ways which are clinically recognizable.

The conducting paths in the brain are more often affected by simple pressure from tumors than by actual destruction, and the removal of the growth or simple relief from pressure may often lead to a surprisingly rapid restoration of function.

For an accurate focal diagnosis, a thorough, early examination is often necessary, for with an advancing lesion symptoms at a distance may greatly confuse the clinical picture. A considerable percentage of cases that present themselves for surgical treatment are so nearly blind that a study of the visual fields, which should be one of the most helpful localizing signs, is precluded.

From a histological point of view the classification of brain tumors is most unsatisfactory, and the general behavior and manner of growth of many of them does not conform with accepted views. Some gliomata may be definitely encapsu-

lated and favorable for operative removal, and many tumors of this supposedly malignant type may undergo cystic degeneration or gelatinous transformation.

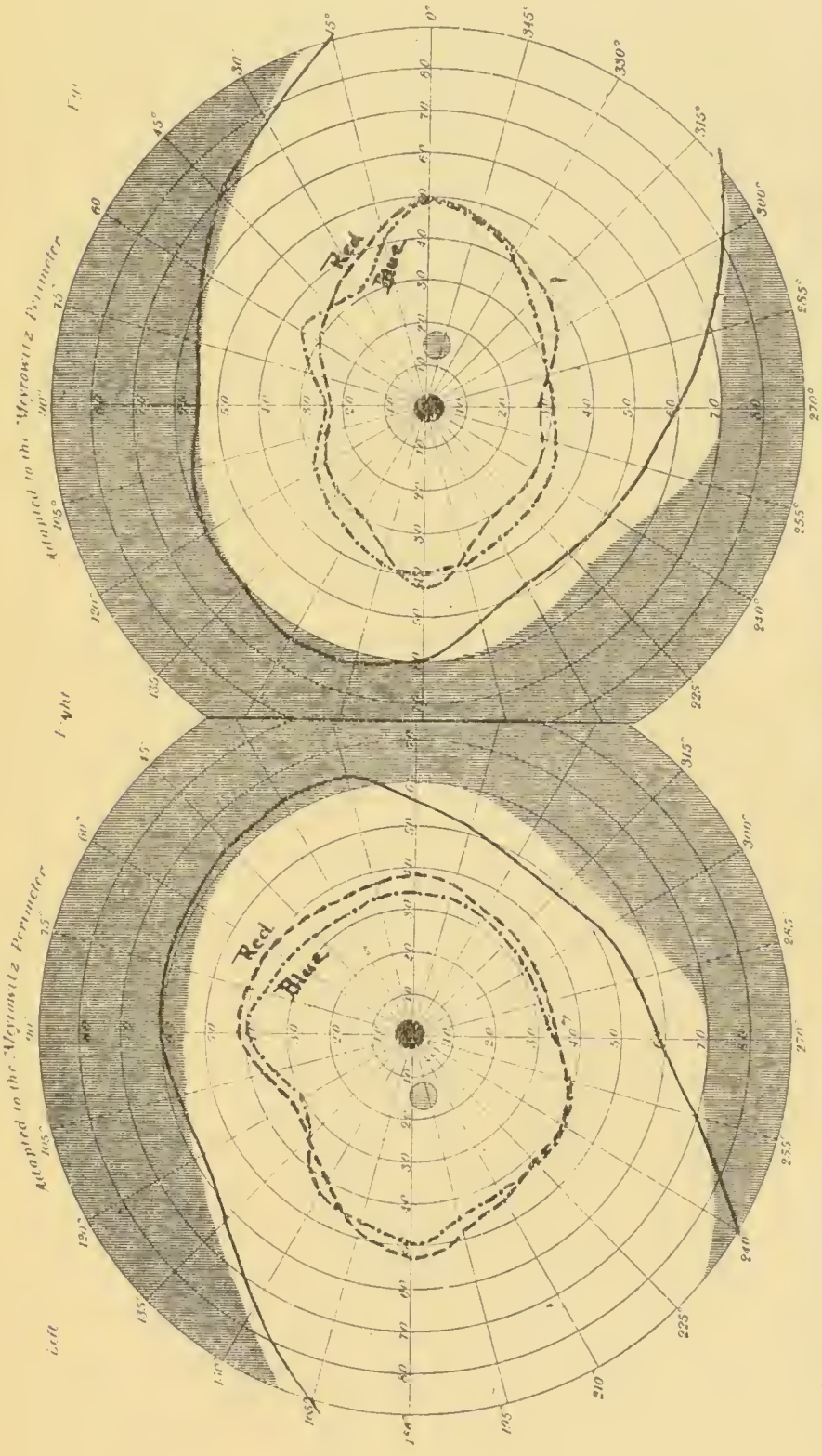

FIG. 1. Visual fields, taken a few days before operation, of a patient with a low grade of choked disk, headache and focal epilepsy. Note the typical interlacing with considerable inversion of the boundaries for blue with no alteration of the fields for form (white).

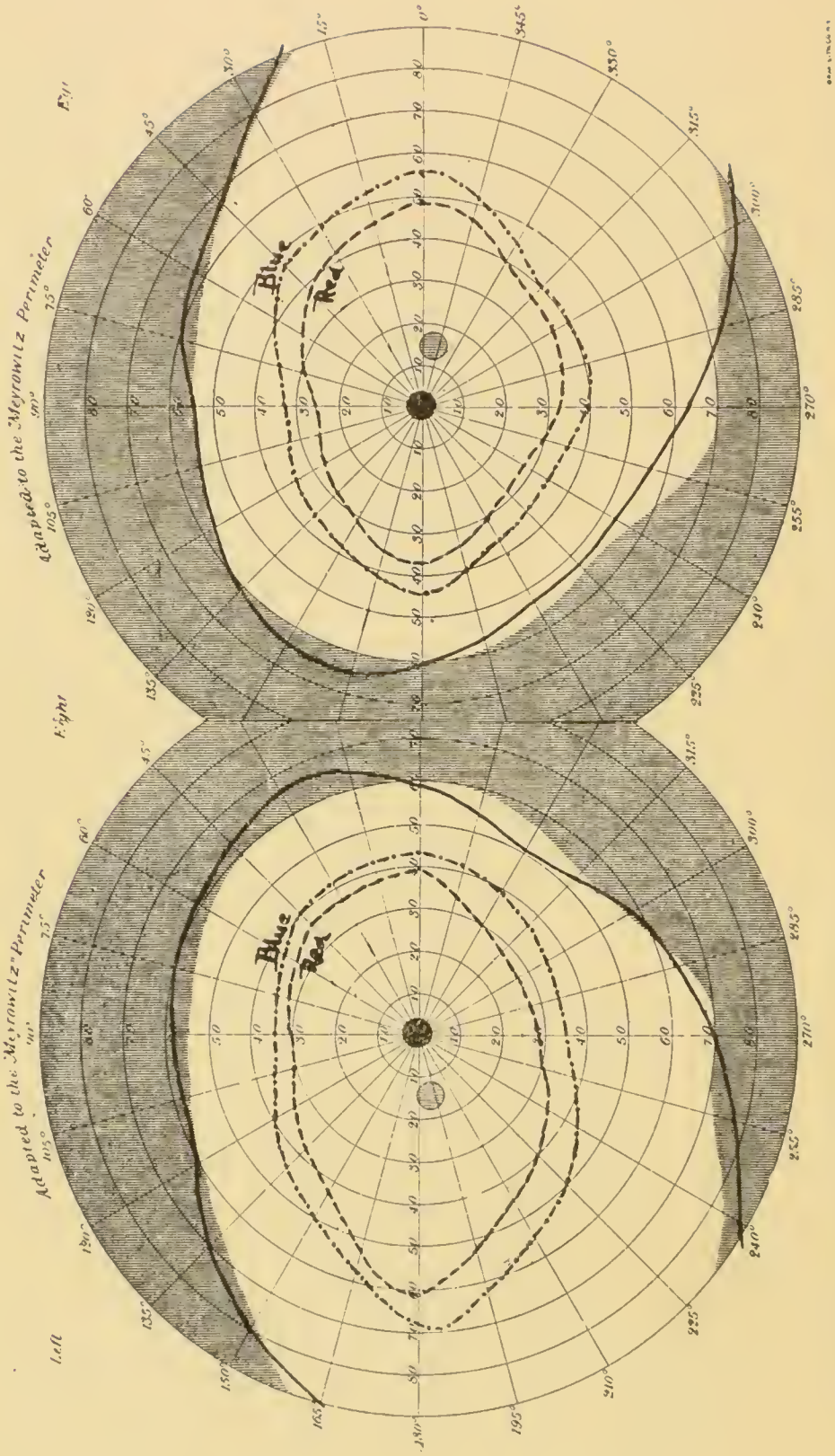

FIG. 2. Visual fields of same patient eight days after an exploratory craniotomy combined with subtemporal decompression as the tumor was not disclosed. Note restoration of normal color outlines following relief of pressure symptoms.

The Etiology of Tumors Considered from the Standpoint of Congenital Tumors and Tumors Following Repeated Injuries.*

BY S. B. WOLBACH, M.D.,

ALBANY, N. Y.,

Director of the Bender Laboratory.

Up to the present time, four important hypotheses of tumor origin have been advanced: those of Cohnheim, Ribbert and Von Hansemann, and that of the parasitic origin of tumors. These hypotheses are important because each one has stimulated investigation and so has indirectly contributed to the advancement of knowledge in this great subject.

The hypothesis of parasitic origin of tumors has had its day, because, subject to direct experimental test, it has been found incapable of proof and inadequate to explain many facts disclosed in recent investigations.

I shall state briefly and in broad terms the hypotheses of Cohnheim, Ribbert and Von Hansemann because the contents of this paper deal with each one and because each one has a basis founded upon established biological facts and principles.

Cohnheim's hypothesis is that tumors take origin from cells " which in the course of development have been displaced from their normal relationship, or have failed to undergo a normal atrophy." The existence of groups of such cells or " embryonal rests " in the infant and adult bodies is not a rare occurrence, as I shall show below. This hypothesis did not attempt to explain why the isolated cells take on aberrant growth, or why so few out of the many that are constantly encountered in pathological work become malignant.

Ribbert's hypothesis at first was essentially an expansion of Cohnheim's and included, as starting points for tumors, postnatal displacements of cells. Recently he has further extended his hypothesis to the effect that mechanical isolation of cells is

* A lecture under the auspices of the Cancer Commission of Harvard University, March 4, 1909.

not necessary, and gives as the essential feature the physiological isolation of cells through changed function. His hypothesis thus is broadened to include the origin of tumors from cells once a part of normal structures. He explains the origin of carcinoma by the physiological isolation of epithelial cells brought about by primary changes in the supporting connective tissue; and has applied this explanation to the origin of cancer from embryonal rests as well as from normal structures.

Von Hansemann's hypothesis states that the tumor cell is one that has suffered modification characterized by a loss of the power of differentiation and the acquisition of increased powers of growth. This condition he calls anaplasia. The hypothesis does not explain why this change should occur.

CONGENITAL TUMORS.

The most important feature in the consideration of congenital tumors is the fact of their occurrence. There are now hundreds of cases on record, including nearly every kind of malignant growth, while less than fifty years ago Virchow wrote in his book, " Die Krankhaften Geschwulste," that " hardly any cases of congenital sarcoma are known."

The congenital tumors may be divided into four classes: (1) the teratomata; (2) the mixed tumors; (3) malignant tumors of specific structures, which closely resemble normal tissues, and (4) true, simple tumors, including carcinoma and sarcoma.

The facts known about the origin of the congenital tumors apply to the first three classes and support the hypothesis of Cohnheim.

Teratomata, which group includes those cases of an imperfect fetus developing in the body of a more or less perfect fetus, are known to take origin from cells of a very early embryonic period, i. e., the blastomeres, which are cells capable of giving rise to all types of tissues. Misplacement of blastomeres has been observed and may be produced experimentally in the lower animals, causing the production of monstrosities. In this way the occurrence of teratomata, containing representatives of every tissue in the body, in such places as the mediastinum and cranium, as well as in the ovaries and testicles, may be accounted for.

The origin of the simpler mixed tumors, such as those of the kidney and parotid gland, may be traced to isolation of cells at a later period of growth. For example, the kidney develops by a very complicated process, as follows: The Wolffian body, or primitive kidney region, gives rise first to the myotome, from which at a later period the nephrotome, or matrix for the kidney tissues, arises. The myotome also gives rise to the sclerotome, from which develop striated muscle, bone and connective tissue. The finding of tumors in the kidney containing bone, muscle and primitive kidney tissues can only be explained by the assumption that cells capable of giving rise to these various tissues, i. e., those of the myotome, have been isolated and carried along in the developing kidney. A similar explanation is offered for the origin of the mixed tumors of the parotid to the effect that cells of the primitive epiblast, whence develop bone, cartilage and gland structures, have become isolated and included in the region of the developing parotid gland.

In the human, isolated groups of cells, or embryonal rests, have been found in many regions. In the skin, rests occur as pigmented nevi, or moles. Malignant tumors frequently take origin in these moles. In the female genitalia, rests are of very frequent occurrence, and, according to their location, may be referred back to the Wolffian ducts or to Müller's ducts. Teratomata of the ovaries in infants have been described, and sarcoma of the vagina is most frequent in infancy and early childhood, and has been found at birth. These "sarcomata" of the vagina may contain nests of epithelium and striped muscle. Recurrence after removal is common. Invasion of surrounding tissue is the rule, while metastases are rare.

Malignant tumors in infants in the region of the sacrum and coccyx are relatively frequent. Many of them contain tissue of nervous origin and hence must arise from remains of the neural canal. Such remains have been demonstrated in otherwise normal fetuses by Dr. Mallory.

It is not rare to find at autopsy small inclusions of adrenal tissue in the kidney, and this furnishes another instance of demonstrable rests of tissue in an organ where malignant tumors of similar tissue are of frequent occurrence.

It is almost certain that the multiple chondromata take origin in rests of cartilage tissue, rests of which have been demonstrated.

In addition to the evidence supporting Cohnheim's hypothesis, to be found in the occurrence of rests of tissue of a type in organs where malignant tumors representing a similar type of tissue are frequently found, we have the further evidence of the association of congenital tumors with anatomical defects of development.

Twenty-five cases of mixed tumors of the kidney have been associated with congenital defects of the brain (" hypertrophic tuberous cerebral sclerosis "). Congenital tumors of heart muscle are usually associated with other congenital defects such as spina bifida and cerebral sclerosis. One case which I reported was associated with spina bifida and multiple nests of neuroglia tissue in the meninges of the spinal cord. A large proportion of supernumerary and accessory ovaries have been the seat of tumors. One case of a congenital heart lesion (an imperfect interventricular septum) in a young adult, autopsied at the Boston City Hospital, had a myoma of the intestine.

Certain tumors are more common in infants and children than in adults. These are the tumors of the eye (retinal glioma) and the mixed tumors of the kidney. They are also by far the commonest tumor of infants, which, considering the complicated development of these organs on the basis of Cohnheim's hypothesis, is to be expected.

True sarcoma and carcinoma are rare in infants. Malignant tumors in infants are generally reported as sarcomata, probably simply because the cells are of indeterminate type, representing as they do cells of an early period of development. A fact of interest is that many cases of carcinoma of the appendix have occurred during, or before, the adolescent period, and the majority before the age of forty. As the appendix is a rudimentary organ, it seems rational that the epithelial tumors occurring there should make their appearance in early life.

The above cursory treatment of the subject of congenital tumors is sufficient to show that Cohnheim's hypothesis is strongly supported. The most frequent occurrence of tumors in early life in organs of very complicated development, as the eye and kidney; the association of congenital tumors with anatomical malformations or vice versa; and, finally, the frequently demonstrated presence of remains of embryonal structures in many locations, all urge the belief that the tumors

of early life develop from embryonal rests. But so far nothing has been offered in explanation why these isolated cells and structures take on malignant properties. Ribbert has suggested that the products of metabolism of such isolated cells may influence the surrounding connective tissue in a deleterious manner and thus excite a series of changes which by their reaction upon the cells of the rest may, after months or years, bring about malignant properties. Some support for Ribbert's suggestion may possibly be found in the matter presented in the second part of this paper.

TUMORS FOLLOWING REPEATED INJURIES.

The term "injuries" is used here in a very broad sense. Under this title I shall discuss the association of carcinoma with well-known pathological processes and those carcinomata associated with unusual occupations and peculiar practices. For the purposes of approach and introduction, it is now necessary to consider some of the effects upon epithelium of pathological processes of long duration.

METAPLASIA OF EPITHELIUM.

The so-called metaplasia of epithelium as a result of pathological processes consists chiefly in the change from the mucous variety of epithelium to the stratified squamous type and in the production of exuberant growth with altered structural and cell characteristics.

The simplest example of the change from the mucous to the squamous type is seen in eversion of the uterus, where the mucous membrane after a time changes from the columnar type to a stratified squamous epithelium of which the outer layers may show a definite horny change like that found in the normal epidermis.

In ordinary chronic inflammatory processes, including suppuration, a similar change may occur in certain organs. The conjunctiva may become thick and stratified in chronic conjunctivitis. The mucous membrane of the turbinate bones and of the accessory sinuses of the nose, particularly in the antrum of Highmore, may undergo a similar change in chronic inflammations. In the middle ear, in chronic suppurative processes with granulation tissue, the production of horny squamous epithelium

may be so great as to give rise to solid tumor-like masses composed of horny desquamated epithelium, the so-called pearl tumors, or cholesteatomata. Similar accumulations of horny epithelium have been found in the ureters in the presence of calculi. In the gall bladder, in chronic inflammation, with or without the presence of calculi, the mucous membrane may become transformed to the squamous type and there may also be small pendulous outgrowths (condyloma).

In chronic inflammations of the larynx, trachea and bronchi, patches of squamous epithelium are often found, and in a few instances where such patches in the larynx could be observed, papillomata and carcinoma have been found to arise in these areas. At autopsy, cases of benign and malignant epithelial growths of the respiratory tract have been found associated with multiple patches of squamous epithelium.

The change from squamous epithelium to the columnar type has been found in the bladder and in the membranous and prostatic urethra, often attended with papillary outgrowths. In the bladder these papillary epithelial growths are quite common following chronic cystitis of many years' duration, and not rarely they are associated with malignant, epithelial growths.

Experimentally, the mucous membrane of the stomach in rabbits has been made to undergo the change from the normal into stratified squamous epithelium.

HETEROTROPHIC PROLIFERATION OF EPITHELIUM IN CHRONIC INFLAMMATORY PROCESSES.

The facts presented under this heading are taken from a paper by Lubarsch, who defines the term " heterotrophic proliferation " as meaning the occurrence of epithelium where it positively does not belong. In speaking of the intestinal tract, he limits the application of the term to those cases where the epithelium is found between the bundles of the muscularis mucosæ or completely beneath it.

Every pathologist is familiar with this condition and with the difficulty of distinguishing microscopically between this inflammatory growth and carcinoma. Usually the history of the case and the macroscopic appearance make the diagnosis easy. The occurrence of heterotrophic growths is most com-

mon in the aged and is always the result of deep-seated chronic inflammatory processes. Usually gland-like structures are reproduced in the down growths. There may be separation of the down growth from the surface epithelium, and the cells may or may not show evidences of growth.

In the series of cases presented by Lubarsch, there were 52 cases of heterotrophic proliferation of the stomach epithelium, attended either by hypertrophy or atrophy of the mucosa as a whole; the average age was sixty-two to sixty-four years. From the intestinal tract there were 32 cases, all associated with deep-seated inflammatory processes, such as tuberculosis and dysentery. The average age was fifty years.

From the gall bladder there were 36 cases, with an average of fifty-six years. Nine of these cases showed such extreme thickening and down growth that the condition was a difficult one to distinguish from tumor, except for the obvious association with chronic inflammatory processes.

These results were carefully controlled by Lubarsch, who excluded the possibility of embryonal rests being mistaken for islands of heterotrophic proliferation by a thorough search for embryonal rests in normal organs. The results were practically negative for the organs examined, which were the gall bladder, stomach, appendix, cecum, anus and rectum.

THE ASSOCIATION OF METAPLASIA AND HETEROTROPHIC PROLIFERATION OF EPITHELIUM WITH CARCINOMA.

There is a fairly well-established association of carcinoma of the respiratory passages and of the urinary bladder with processes attended by metaplasia of the epithelium.

In Lubarsch's series, 59% of the cases showing heterotrophic proliferation had carcinoma in some organ. There were 9 cases of carcinoma of the esophagus, 7 of the stomach, 4 of the intestines, 3 of the uterus, 2 of the gall bladder and 1 each of the pharynx, bile ducts and lung. In 17 cases heterotrophic proliferation in an organ was associated with carcinoma of the same organ.

Since heterotrophic proliferation is a condition found in old age, and carcinoma is essentially a disease of old age, Lubarsch expresses the opinion that the one precedes the other.

From the pathological side there is a fairly well-established association between epithelial changes produced by long-standing inflammatory processes and the occurrence of carcinoma. I shall now take up the consideration of cases in which the association is clinical, though in some instances corroborated by pathological investigation.

CARCINOMA FOLLOWING WELL-KNOWN PATHOLOGICAL PROCESSES.

Tumors of all varieties have repeatedly been referred back to traumatism as an exciting cause. It is needless to consider seriously any of the single published cases, of which there are a great number, attributing the cause of a malignant growth to a single traumatism. However, there is among clinicians a firm belief that certain pathological conditions are responsible for tumor production. The very superficial investigation I have made into the foundations for this belief indicate that the question is an important one and worthy of very careful investigation by pathologists engaged in cancer research.

Carcinoma of the uterus. — Cullen, in his book on "Cancer of the Uterus," discusses the etiology from the standpoints of trauma, heredity, embryonic cell inclusion, Ribbert's theory, parasitic origin and cancer as a primary disease of epithelium. From his careful study of a small number of cases of squamous-cell carcinoma of the cervix (fourteen) he comes to the conclusion that "the injuries incidental to labor have a potent influence in the development of this variety of cancer." This seems to be the opinion of many eminent and conservative gynecologists. The association of cancer of the body of the uterus and pregnancy is not so apparent, though Cullen's series of 19 carefully-studied cases shows an apparent connection between childbearing and cancer of the body of the uterus.

Carcinoma of the stomach, gall bladder and bronchi. — Support for the belief of origin of carcinoma of these organs in ordinary pathological processes is furnished by the pathological studies of Haberfeld. From 20,000 autopsies there were 662 cases of carcinoma of the stomach, 106, or 16%, of which could be proved to have been preceded by ulcer. Inasmuch as there was no way of determining the precedence of ulcer in the other cases, he concludes that there must be a connection between carcinoma and ulcer of the stomach. The connection between cholelithi-

asis and carcinoma of the gall bladder is more evident. Out of 265 cases of gallstones in 20,000 autopsies, 27% were in males, 73% in females. In the same series of autopsies there were 164 cases of carcinoma of the gall bladder, of which 27% were in males and 73% in females. In 98 cases of gall-bladder carcinoma collected from other authors, there were 68 cases with cholelithiasis, an average of 70%. Haberfeld argues that gallstones were found almost without exception in cases of primary carcinoma of the bladder, while in secondary carcinoma they are very rare. The strongest argument he advances for the connection between the two conditions is that the ratio of carcinoma of the gall bladder in the two sexes is exactly the same as in the case of gallstones. He concludes that the relationship of carcinoma to gallstones is inevitable.

As an introduction to the statistics of carcinoma of the bronchi, Haberfeld calls attention to the fact that the right lung during youth is more often affected by diseases than the left. This he largely attributes to the anatomy of the bronchi, and lays stress upon the straighter line made by the right primary bronchus with the trachea. He thinks that the right bronchi and lung are more exposed to injurious agents than the left. The type of injury is not that directly due to inhalation of solid particles and injurious gases, but to the resultant secondary infectious processes. Since males are more exposed than females, cancer of the bronchi should be more common in males, and this is shown by the 193 cases he collected from his own series and those of four other authors, in which 155 were in males and 38 in females. The more frequent occurrence of carcinoma in the right side also supports the belief in the connection between injury and carcinoma. Thus, out of 146 cases collected, 94 were primary on the right side, 41 on the left side. In 9 cases there was bilateral carcinoma.

Histologically, the 68 cases in Haberfeld's series were mostly of the squamous-cell type, so that the argument is suggested that the same causes that produce the squamous-cell metaplasia of the bronchial epithelium are responsible for the production of carcinoma.

Carcinoma of the breast. — The association of chronic mastitis and carcinoma of the breast is firmly fixed in the minds of sur-

geons, and the pathologist when examining microscopically cases of chronic mastitis is often confronted by masses of epithelial cells hard to distinguish from carcinoma. In these cases there may be marked epithelial proliferation and changes in cell characteristics with the production of cell masses which resemble carcinoma in every way, except in evidences of invasion.

A recent analysis of 100 cases of carcinoma of the breast by Leaf gives the following results: Eighty-four per cent were married women; the remaining 16% were unmarried. Seventy-one per cent of the 100 cases gave histories of abnormal lactation characterized either by over-lactation or under-lactation. Thirty-five per cent showed a definite history of injury, and in 32% the carcinoma developed in the injured side. The average duration of time after injury before the carcinoma was noticed was three years and two months. Twenty-three per cent of the 100 cases had a family history of carcinoma.

Carcinoma of the penis. — Chronic balanitis is invariably given as the most important etiological factor in the production of carcinoma of the penis. The statistical *evidence* for this belief is wholly of a negative character, consisting of the known immunity of circumcised races to carcinoma of the penis. In 100 cases from the Massachusetts General Hospital, none were in Jews. Bashford, in the third report of the Imperial Fund for Cancer Research, says that carcinoma of the penis is practically unknown in Mohammedan races which practice circumcision.

Carcinoma following lupus. — Recently, many cases of epidermoid carcinoma and a few cases of sarcoma have been reported in lupus patients. The tumors develop in the affected areas after many years' duration of the disease. The number of cases reported is too great to admit of explanation by coincidence. In one series of cases of lupus (Wild), five out of every fifty developed carcinoma. Furthermore, the very early age in which epidermoid carcinoma makes its appearance in lupus patients and the frequent occurrence in females are additional evidence of relationship.

In addition to the above conditions associated with carcinoma and capable of statistical support, there are numerous other pathological processes which have long been associated with tumor production.

Tumors of the colon are more common at the flexures, and the explanation usually given is that the feces remain there for a longer time, giving rise to greater trauma and absorption there than elsewhere. The effects of heat and volatile substances from tobacco smoking are popularly supposed to contribute to carcinoma production in the mouth and lips. The name "scar cancer" has arisen from the apparently frequent development of cancer in scar tissue. In syphilitics the development of cancers in patches of leucoplakia in the mouth has been sufficiently frequent to establish a belief in the etiological relationship. Finally, we have the association of very simple chronic inflammatory processes with carcinoma production in cases of chronic osteomyelitis of many years' duration when attended by a discharging sinus.

CARCINOMA ASSOCIATED WITH UNUSUAL OCCUPATIONS AND PRACTICES.

Perhaps the best known of all occupations associated with carcinoma is that of chimney sweeps. The type of carcinoma is the epidermoid or epithelioma, which usually makes its first appearance upon the scrotum. The affection has been most common in England, and its rarity in other countries has been used as an argument against the causal relationship of the occupation to the disease. A recent paper by Butlin discloses the fact that the sweeps in England are notoriously careless in protecting their person, while the sweeps of continental countries are more cleanly and wear a special dress adapted to protect them from the soot while engaged in their work. Chimney sweep's carcinoma makes its appearance after many years of service and is always preceded by thickening of the skin, keratoses and persistent ulceration.

Carcinoma of the scrotum is a rare disease. During five years at the Boston City Hospital, 1881 to 1887, there was but 1 case. In twenty years preceding 1887, 48 cases were collected in London, of which 38 or 39 were in sweeps. In 4 of the remainder, the occupation was not determined. Of 29 cases in sweeps from one hospital (St. Bartholomew's), 21 were below the age of fifty. Two cases were recorded in men below the age of thirty. Oliver, in his book on "Diseases of Occupation," states that the mortality among chimney sweeps from carci-

noma for three years preceding 1902 compared with other occupations involving manual work was as 133 to 63. Another set of statistics gives the ratio as 156 to 44. These figures are significant when we take into consideration that cancer of the scrotum is a very rare disease, and though it may be true that the mortality among sweeps from this disease is no greater than the general mortality among women from carcinoma of corresponding parts, the vulva, as claimed by Roger Williams, the significance is not diminished. Carcinoma of the vulva is not a very rare disease, and, therefore, the comparison is not a valid one.

In fact, among all occupations where the handling of products of combustion of coal is a feature, many cases of chronic dermatitis leading to keratoses and carcinoma occur. This association is so frequent that it has become of great clinical importance. The occupations besides that of chimney sweeping where soot or distillation products of coal are handled are, gardening, where soot is used to sprinkle plant beds; workers in carbon factories; and tar, paraffin and asphalt workers. In all of these occupations the evolution of the disease is the same,— chronic thickening of the skin, keratoses, ulceration and, finally, carcinoma. In all, the exposed parts only become affected. In this country a few cases of carcinoma following the usual type of chronic dermatitis have been reported from the National Carbon Works.

Aniline workers. — Workmen engaged in handling aniline oil products are particularly subject to chronic cystitis, which has been fairly well proved to be due to the elimination of aniline derivatives in the urine. After many years of service, a certain proportion develop tumors of the bladder, so that the association between the occupation and the disease has become fixed in medical literature. Up to 1907, 26 cases of bladder tumor have been reported in aniline workers. Twenty of these cases were malignant. The time of exposure varied from five to twenty-nine years. The majority of the tumors are malignant papillary growths. A few have been reported as sarcoma.

Recently I autopsied a case of carcinoma of the bladder in a man who had worked in an aniline works for more than fifteen years. For many years he had had chronic cystitis.

Bilharzia disease. — Bladder tumors are so common in persons with Bilharzia disease that the causal relationship is unques-

tioned. Until recently the nature of these tumors could be questioned, but a recent paper by Goebel, based upon careful pathological investigation, states that 50% are malignant.

Carcinoma of sailors. — A few cases of multiple carcinoma of the face in sailors have been reported by Unna, who, on account of the sequence of chronic dermatitis, keratoses and carcinoma, thinks that the disease is a direct result of exposure in susceptible individuals.

"Kangri" carcinoma. — This is almost the most striking instance we have of carcinoma associated with a definite and peculiar practice. The Kangri is a small earthenware stove employed by the natives of Kashmir and worn attached to the belt beneath their robes. After many years of this practice, a chronic dermatitis results which finally becomes the seat of carcinoma. Closely allied tribes living at lower altitudes, who do not employ this method of keeping warm, do not have this disease. Because of the extreme rarity of carcinoma of the skin of the abdomen, there can be no doubt as to the causal relationship of the practice to the disease. This account is taken from the third report of the Imperial Cancer Research Fund of England.

Two other striking examples of carcinoma associated with definite practices are also taken from the last report of the Imperial Cancer Research Fund. These are the "Horn Core" cancer of cattle, and cancer in women who chew preparations of betel leaves.

The former is an epidermoid carcinoma beginning at the base of the right horn of cattle employed in India for draft purposes. The traction is made by means of a rope attached to the right horn and hence the evident causal relationship. Carcinoma of the cheek in women who chew betel leaves is attributed to the fact that the preparation consisting of betel leaves, lime and other ingredients is constantly kept in one position even during sleeping hours between the teeth and cheek. A causal relationship is indicated by the fact that the tumor develops on the side employed in the practice.

CARCINOMA FOLLOWING X-RAY EXPOSURES.

I have reserved this subject for the last because of its great importance and its bearing upon the value of the other associa-

tions between tumors and preceding processes. Because of the large number of cases, the occurrence in young individuals and the multiplicity of the growths upon exposed parts only, the causal relationship between repeated x-ray exposures and carcinoma cannot be denied. Nor is it denied by any who have investigated the subject with care. New cases are constantly being reported, and the etiological connection between the x-rays and carcinoma of the skin is now accepted in all countries.

The x-ray carcinoma is the first experimental carcinoma. The subjects have been men more or less constantly exposed to the x-rays during working hours. The evolution of the disease has been carefully observed and is practically constant in all cases. A few of the victims have been patients subjected to many exposures during several years. Up to the time of writing, thirty-six cases of carcinoma have been collected and verified by microscopic examination. The majority are cases of young individuals. Many have ended fatally from metastases. In all cases the tumors have been multiple upon exposed portions of the body only, — hands, arms and face. X-ray carcinoma, then, is characterized by its occurrence in young individuals and by its malignancy. It develops in skin which has been for several years the seat of a chronic dermatitis characterized by telangiectases and keratoses.

The evolution is in many respects similar to the evolution of carcinoma in sailors, chimney sweeps, and Kangri carcinoma, and great stress must be laid upon the fact that, where a large number of cases of carcinoma are associated with a given occupation or practice, the tumors always develop on the part of the body exposed to the injurious agent.

I have had an opportunity of making a careful study of cases of chronic x-ray dermatitis, the material for which was supplied by Dr. C. A. Porter. The results of this study showed that the chief effects of the x-rays were upon the deep tissues of the skin, connective tissues, smooth muscle and endothelium. There is repeated destruction of tissue and repair until the development of obliterative changes in the vessels prevents normal repair. Then comes a stage when the structure of the skin greatly changes, during which the epithelium is constantly forced to proliferate in order to repair small defects caused by the necrosis

of the underlying tissue. The epithelium is likewise probably subjected to very marked changes in nutrition. The importance of these findings is greatly increased by the fact that in a few cases where patients were subjected to a long period of exposures to the x-rays, carcinoma did not develop for a long time afterwards,— usually several years. This so-called latent period is against believing that the direct action of the rays is the cause of the tumor production. The constant severe changes existing over this period in the deeper layers of the skin have a marked effect upon the epidermis, as I have proved, and are, therefore, probably responsible for the acquisition of new properties on the part of the epidermis.

The change in the epidermis is perhaps best regarded not as the acquision of new properties, but as a reversion to an earlier type in which the property of differentiation has not been acquired while the growth capacity is at its maximum.

Other investigators of x-ray lesions and carcinoma, notably Unna, Wyss and Linser, have come to a similar conclusion regarding the effects of the rays upon the skin. All have found the chief effects to be in the tissues below the epidermis.

The conclusions drawn by myself and other workers in regard to the evolution of the x-ray carcinoma are of great importance because of the support they necessarily give to Ribbert's hypothesis.

Goebel, in his investigation of bladder tumors in Bilharzia disease, has traced the first process back to the stoppage of vessels by the ova of the parasites. The first effect is, therefore, necrosis without sepsis and followed by imperfect repair. Proliferation of the epithelium is here also secondary to connective tissue changes. It is maintained by a long-continued, constantly repeated aseptic inflammation caused by the ova of the Bilharzia parasite.

Goebel finds analogies between the processes in Bilharzia disease and those observed in aniline workers, tobacco smokers, chimney sweeps, etc.

There is unquestionably a great similarity between the processes in Bilharzia disease of the bladder and the x-ray dermatitis.

SUMMARY.

In the first part of this paper I have endeavored to present a few data which support the belief that the congenital tumors and tumors of infancy and early childhood most commonly take origin from isolated or misplaced cells. At least we have very positive evidence that certain tumors, such as the teratomata, hypernephromata, mixed tumors of the kidney and parotid and the retinal tumors arise from such errors of development. In the second part, I have endeavored to show that in the cases of x-ray carcinoma and a few other instances, such as Bilharzia disease and Kangri carcinoma, there is a proved causal relationship between malignant tumors and antecedent pathological processes. The more peculiar the source of the injury, the greater is the value of the evidence when the association is marked by a strikingly large number of cases. The similarity in the evolution of the skin carcinoma in widely different kinds of exposures points to a common underlying process whatever the nature of the injurious agent. In the cases of x-ray carcinoma, and Bilharzia carcinoma, there is a proved similar antecedent pathological process. X-ray carcinoma is to be regarded as the first instance of an experimentally produced malignant tumor. Its occurrence following definite lesions of the skin, of a continuous and progressive character, places the whole subject of carcinomata following repeated injuries upon a firm basis. It designates this field of investigation as the most promising one for research into the origin of carcinoma, because we have at least one and perhaps several examples of proved causal relationship.

The facts presented do not speak for belief in simple trauma as a cause for tumor production. They do indicate that long-continued progressive lesions of connective tissue supporting epithelium are responsible for the acquisition of malignant properties by the epithelium. This belief is not so far removed as it would at first appear from the hypothesis of Von Hansemann, who believes that the malignant property of epithelium is a primary disease. There is no incompatibility in a theory which holds to the idea that similar properties may be acquired by years of changed environment and nutrition.

Finally, it may be said that no series of experiments upon animals, in the attempt to produce tumors, has ever been

carried out which in any way approached duplication of those conditions we find in man associated with the production of cancer. The element of time is perhaps the most important factor. Many years always elapse between the onset of the antecedent pathological process and the occurrence of cancer. In the case of the x-rays ten years is perhaps the shortest period. But the magnitude of the problem and the value of the results should justify the expenditure of time and money necessary to more adequately investigate this field of the cancer problem.

REFERENCES.

Ribbert: Geschwulstlehre. Bonn, 1904.

Ibid: Beiträge zur Entstehung der Geschwulste. Bonn, 1906.

Ibid: Zweite Ergänzung. Bonn, 1907.

Ibid: Dritte Ergänzung. Bonn, 1908.

Adami: The Principles of Pathology, vol. i, 1908.

Williams: Natural History of Cancer. 1908.

Oliver: Diseases of Occupation. 1908.

Gœbel: Ueber Congenitales Femur Sarcom geheilt durch operative und Röntgenbehandlung nebst Bemerkungen über congenitale Maligne Tumoren. Arch. für klin. Chir., Berlin, lxxxviii, 1908.

Albrecht: Ein Fall von angeborenen Fibrosarcom der Haut. Jahresb. u. Arb. d. ii Chir. klin. z. Wien, Berlin, 1906.

Walter: Abstract in Lubarsch und Ostertag, vol. x, 1904–1905.

Brienl: *Ibid.*

Herth: *Ibid.*

Pernet: Multiple Congenital Sarcoma of the Skin. Trans. Path. Soc. London, 1902.

Frank: Papillary Cystadenoma in a Supernumerary Ovary. Surg., Gynec. and Obstet., vol. viii, no. 1909.

Wolbach: Congenital Rhabdomyoma of the Heart. Jour. Med. Research, vol. xvi, no. 3.

Bonney: The Connective Tissue in Carcinoma and in Certain Inflammatory States that Precede its Onset. Lancet, May 16, 23 and 30, 1908.

Lubarsch: Ueber heterotrope Epithelwucherungen und Krebs. Verhandl. d. Deut. Path. Gesell., 1906.

Fütterer: Ueber Epithelmetaplasie. Lubarsch und Ostertag, 1903, part ii.

Bashford: The Ethnological Distribution of Cancer. Third Scientific Report on the Investigations of the Imperial Cancer Research Fund. London, 1908.

Barney: Cancer of the Penis. Ann. Surg., 1907.

Zieler: Ueber die unter den Namen "Paget's Disease of the Nipple" bekannte Hautkrankheit und ihre Beziehungen zum Karzinom. Virchow's Arch., Bd. 177, heft 2.

Leaf: The Causes of Cancer of the Breast (Clinical), with Some Remarks upon the Connection between Irritation and the Production of Malignant Growth (Experimental). Zeitschr. für Krebsforsch., 1907.

Tauffer: Sarcom auf narbig-lupösen Boden. Virchow's Arch., sup. to vol. cli.

Spencer: Cases of Lupus becoming Epithelioma after Repeated Surgical and Prolonged X-Ray Treatment. Trans. Clin. Soc. London, 1906, vol. xxxix.

Wild: The Supervention of Epithelioma upon Lupus Vulgaris. Publications of the University of Manchester, Medical Series No. 8, 1908.

Oliver: Tar and Asphalt Workers' Epithelioma and Chimney Sweeps' Cancer. Brit. Med. Jour., Aug. 22, 1908.

Butlin: Cancer of the Scrotum in Chimney Sweeps and Others. *Ibid.*, June and July, 1892.

Leyberth: Beitrag zur Kenntniss der Blasengeschwülste bei Anilin arbeitern. Münch. Med. Wochenschr., Bd. 54, part ii, 1907.

Lucke: Epithelioma in Carbon Workers. Cleveland Med. Jour., 1907, vol. vi.

Unna: Carcinoma of Sailors. Histopathology of the Diseases of the Skin.

Haberfeld: Zur Statistik und Aetiologie des Carcinoma des Magens, der Gallenwege und Bronchien. Zeitschr. für Krebsforsch., Bd. vii, 1908.

Goebel: Ueber bei die Bilharziakrankheit vorkommenden Blasentumoren mit besonderer Berücksichtigung des Carcinoms. *Ibid.*, Bd. iii, heft. 4.

Wyss: Zur Entstehung des Röntgencarcinoms der Haut und zur Entstehung des Carcinoms in Allgemeinen. Beitr. zur klin. Chir., 1906, vol. xlix.

Wyss: Zur Entstehung Primärer Carcinome. Deut. Arch. für Chir., Bd. xciii, heft 6.

Gassmann: Histologische Befunde beim Röntgenulcus am Kaninchen. Arch. für Dermat. u. Syph., 1904, heft 1.

Linser: Beitrag zur Histologie der Röntgenwirkung auf die normale menschliche Haut. Fortschritte auf d. Gebeite d. Röntgenstrahlen, no. 8, 1904–1905.

Unna: Die Chronische Röntgendermatitis der Radiologen. *Ibid.*

Porter and White: Multiple Carcinomata following Chronic X-Ray Dematitis. Ann. Surg., November, 1902.

The Problem of Cancer Considered from the Standpoint of Immunity.*

BY FREDERICK P. GAY, M.D.,

BOSTON, MASS.,

Instructor in Pathology, Harvard Medical School.

The probability of applying the principles of immunity, determined by studies on bacterial infections, to the problem of cancer was not very great so long as this disease was studied only as it occurred in human beings. The introduction of experimental cancer research in animals through transmissible tumors has made the possibility of combating this disease by means of vaccination or specific serum much more hopeful. In cancer no parasitic etiological factor has as yet been demonstrated, but progress toward a prevention of the disease would seem at the present moment not to be dependent on the discovery of such an agent. We have indeed in rabies and in smallpox two diseases that may be successfully prevented, and, if we regard contagion as the beginning of the disease itself, may be cured, in spite of the fact that we possess little or no exact knowledge as to the etiological agent in either of these maladies. We are not, indeed, it seems to me, primarily interested at the present moment in discovering the cause of cancer, particularly if we may regard the tumor itself as the agent of infection and the body of the host as a culture medium. (Ehrlich.)

It may be well, however, to consider, first, certain agents which have been claimed, and are still being claimed, to be the cause of cancer, and, second, to consider in particular certain accessory etiological factors in the disease.

THEORIES OF CANCER ETIOLOGY.

Bacteria have been described in connection with cancer which have been supposed, by certain authors, to bear an etiological relation to the disease. Doyen still maintains that

* Being a lecture delivered at the Harvard Medical School, March 11, 1909, as one of a series given under the auspices of the Cancer Commission of Harvard University.

his *micrococcus neoformans* is the cause of cancer, and he has attempted to treat the disease in human beings by means of a serum from animals that have been immunized against this coccus. Schmidt and others have described certain yeasts as the cause of cancer and have claimed to demonstrate their presence in cancer tissues. Other authors have attributed the etiological rôle in cancer to a protozoon, and various forms of organisms of this nature have been described in the tissues. Borrel, who is inclined to believe that some protozoon must be the cause of cancer, admits, notwithstanding, that none of the organisms described up to the present time can be considered as proved to bear any relation to the disease; he does, however, regard the protozoon origin as probable on account of the fact that cancer histologically would seem to resemble other forms of supposedly protozoon disease, such as variola, sheep-pox (*clavelée*) and molluscum contagiosum.

Leaving aside these supposed parasitic causes of cancer thus summarily, we may turn to a brief consideration of certain physiological factors or substances in the blood which have been supposed to bear some causal relation to cancer growth. These substances may be grouped under two general headings: Those substances which are supposed to act in some positive manner in causing proliferation of epithelial cells, and those substances the absence of which in animals predisposed to cancer may give rise to the growth of the tumor.

Starling has described the presence of certain "chemical messengers," or "hormons," in the blood, arising usually in one organ, which affect the development of another organ in the body. Starling found that if virgin rabbits were given injections of rabbit embryos, the mammary glands of these animals would hypertrophy, and that the same substances injected into rabbits that had borne young would lead to lactation in addition to the hypertrophy. Loeb has applied our knowledge of these hormons to the study of tumors in an interesting manner. This author found that an injury of the uterine wall in a pregnant guinea pig would lead to a proliferation of decidual tissue at the point of injury. This decidual growth does not occur, however, if the corpora lutea are removed or destroyed before the injury is inflicted. In other words, the corpora lutea apparently form hormons which stimulate growth of decidula

tissue. Spuda noted in certain carcinomata that the growth of epithelium apparently begins first about blood vessels, and he concludes from this observation that there must be present in the blood stream some substance which stimulates its proliferation. This supposition of the presence of some stimulating substance in the blood also forms the basis of Fischer's theory of "attraxins." These attraxins are supposedly chemeotactic substances in the blood which stimulate the growth of epithelial cells. Fischer has attempted to produce such overgrowth by injections of sudan oil, but offers no distinct confirmatory evidence as to the presence of such stimulating substances in the animal body.

When we turn to the negative physiological influences which have been supposed to contribute to the growth of malignant tumors, we find that Edel supposed the existence of certain normal substances in the blood which inhibit epithelial proliferation. He would regard the removal of these inhibiting substances as a primary cause in the growth of malignant tumors, and he suggests that normal human serum be injected in order to supply this deficiency. Such a supposititious lack of normal inhibiting substances is comprised in the theory of Beard, who has suggested the use of an artificial ferment to replace this lacking substance. He has used trypsin in human beings and claims that injections of this substance will kill the abnormal tumor cells without affecting the normal tissue. Von Leyden and Bergall, who have attempted to confirm Beard's results, decided that no such effect was produced by trypsin; but they, in turn, describe a ferment which they have isolated from the liver and which they claim affects only cancer cells. They attribute the growth of cancer to a lack of this hydrolytic ferment which is present in normal individuals.

In conclusion, the ideas of Albrecht and Ehrlich, as to the reason for the growth of cancer cells over the normal cells of the body, may be mentioned. These writers conclude that cancer cells grow more rapidly than normal cells on account of their greater affinity for nutritive substances.

SPONTANEOUS CURE OF CANCER IN HUMAN BEINGS.

Of great practical interest in connection with the possibility of producing an artificial condition of immunity in human beings

afflicted with cancer are observations on the disappearance of both benign and malignant tumors in human beings. Both sarcomata and carcinomata have been reported by Czerny, Reichel, Rotter and others as having spontaneously disappeared. As we shall later see, the transmissible tumors of animals frequently disappear after having grown for a considerable period of time.

EMPIRICAL ATTEMPTS AT SPECIFIC TREATMENT OF CANCER IN HUMAN BEINGS.

Attempts had been made to treat cancer in human beings by more or less specific methods even before any of the exact knowledge which has been acquired from the study of experimental tumors in animals was obtained. Busch commented on the fact that the interoccurrence of erysipelas frequently leads to the disappearance of cancer in a patient suffering from this disease. On the basis of this apparent beneficial effect, Fehleisen treated a number of cases of cancer with cultures of the streptococcus isolated from cases of erysipelas and apparently obtained certain beneficial effects. The dangerous results from the erysipelas itself led temporarily to an abandonment of this method of treatment, but Coley has for several years treated cases of inoperable sarcoma with a toxin derived from the streptococcus of erysipelas, or better still, with this toxin combined with a toxin from the bacillus prodigiosus. He has reported some one hundred cases of inoperable tumor which were either greatly benefited or apparently perfectly cured by this method.

Attempts have been made to produce a specific antiserum for cancer by immunizing animals with cancer cells. Thus Richet and Hericourt immunized dogs and asses with an extract of human cancer and used the serum of these immunized animals in the treatment of the disease. Their results were, however, uniformly negative. Von Dungern's description of a specific epitheliolysin, which he found in the serum of rabbits that had received injections of the ciliated epithelium from the trachea of the cow, gave hope of the possibility of forming such a specific serum for other epithelial cells. We have come, however, through the work of Pearce and others, to regard such cytolytic sera as specific for the animal species that has

furnished the cells rather than for any individual type of cells from such an animal.

THE EXPERIMENTAL STUDY OF TUMORS IN ANIMALS.

Tumors have been described in many mammals. In addition to the tumors of wild animals, tumors have been noted in such domestic animals as the dog, cat, horse, cow, mouse and rat. Tumors are very rare in amphibians and have not been described in reptiles. They do, however, occur in birds and fishes. These tumors of animals are both benign and malignant, and the malignant tumors are characterized by the same peculiarities which accompany the malignant tumors of human beings.

TRANSMISSION OF TUMORS IN ANIMALS.

There is no authentic record of the transmission of a malignant tumor in the human being to another individual. There are, however, cases in which tumors have apparently been transplanted from one part of the body to another in a given individual. Many attempts have been made to transfer the tumors of human beings to animals, and with a few exceptions have been uniformly unsuccessful. Dagonet describes the occurrence of a tumor growth in a rat a year after implanting a metatastic tumor from the lymph gland in man. Werner describes the occurrence of a tumor with metastases in a dog following implantation of a human carcinoma of the jaw. From subsequent observations in animals, we know that, as a general rule, the tumors of one species can never be transplanted in animals of another species.

Nowinski, in 1876, succeeded in transferring a nasal tumor of the dog to another dog. In 1889, Morau transferred a carcinoma of the mouse through seventeen successive generations in other mice. In 1901, Loeb described a sarcoma of the rat which was transmissible to other rats but which finally died out. In the same year Jensen described a large series of experiments with a mouse carcinoma, and he succeeded through a number of successive generations in transplanting his tumor successfully in 50% of the animals inoculated.

Since the description of these tumors, numerous tumors of mice and several tumors of the rat and dog have been described and studied by experimental methods. Many of these tumors

show the characteristics of real malignancy in that they produce metastases which lead to the death of the animal.

Spontaneous tumors undoubtedly occur much more frequently in animals than was at first suspected. Whereas, a few years ago, Bashford made the statement that spontaneous tumors in mice occur in only 12 individuals out of 30,000, more careful observation through the entire life history of these animals has led us to believe that such tumors are much more common. Tyzzer, for example, has found that spontaneous tumors occur in his mice in at least 5% of all the animals. The success in transplanting these spontaneous malignant tumors of animals varies markedly with the individual technic of the observer. Ehrlich found that 11 out of 94 malignant tumors were transplantable. Certain types of tumors are much more readily transplantable than others. Ehrlich found, for example, that, in his experience, only 8% of the hemorrhagic tumors could be transmitted to other animals. That the individual technic in transplanting is a matter of primary importance as to the percentage in which these tumors take has recently been evident by the work of Gierke and of Murray. These authors succeeded in transplanting 37 out of 48 hemorrhagic tumors similar to those described by Ehrlich. They attribute the difference in results to the fact that Ehrlich used much more of the tumor substance in transplanting than they did.

There are certain general factors apart from individual technic which must be considered in drawing any conclusions from experiments with transmissible tumors of animals. There are present, indeed, two sets of varying factors, one set dependent on the animals inoculated and the other on the tumor used for inoculation.

It has been the general experience of workers in this field that young animals take the tumor better than old ones. There are very marked differences between races of the same animal species in susceptibility to a given tumor. Thus, Jensen found that whereas his tumor took well in white mice, it took in a much smaller percentage of cases in gray mice. Harland has found not only differences in different races of mice, but determined that a change of environment would lead to a different resistance in a given race. He found that if he removed Berlin

mice to Norway, they failed to take the Ehrlich tumor, whereas, in Berlin, they were very susceptible to it. In addition to variations in race and environment, the probable differences in individual resistance of animals may be mentioned. The fact that certain animals of a given lot fail to take an implanted tumor, whereas others do take it, may be attributed, as Jensen has done, to the occurrence of a natural immunity in the "negative" animals.

The tumor used for implantation may vary remarkably in "virulence" during successive generations. A tumor which takes in 100% of cases when first transplanted, may, after several successive generations, take in only 40 or 50%. It is probable, also, that individual parts of a given tumor vary in their virulence. The point of inoculation of the tumor is also of considerable importance. Thus Bashford, Murray and Cramer have shown that if the tumor is implanted in the axilla, many more animals will take than when the tumor is implanted on the dorsal surface of the animal. This difference they attribute to the greater vascularity of the former region. We have already seen that variation in the amount of tumor inoculated was the cause of the difference in results between Ehrlich and Gierke in their transplantations of hemorrhagic tumors. This factor of the amount inoculated is also of importance in the experiments for the production of an artificial immunity. Tumors may change markedly in cellular type during successive generations. Thus Loeb, Ehrlich and others have described the transformation of a carcinomatous tumor into a sarcoma, and Flexner and Jobling have described transformation of a sarcoma of the rat into a carcinoma. Apolant has mentioned that carcinomata of the mouse grown in partially immunized animals may become adenomatous in structure. Such changes as these in cellular type are of undoubted importance in the virulence of the tumor. The age of the tumor is of some importance in the percentage of successful implantations. It is in general agreed that old tumors are better than young tumors, owing perhaps to the fact that they contain more calcium. (Clowes and Bæslack.) Lewin, by picking the tumors which grew best, succeeded in getting a more virulent strain. In some experiments of my own, by successive implantation from the metastases of tumors instead of from the original inoculated

tumor, I obtained a tumor which was more virulent, as indicated by the fact that it grew more rapidly and produced metastasis sooner.

IMMUNITY IN EXPERIMENTAL CANCER.

Jensen attributed the failure of 50% of his mice to take the tumor to the existence of a condition of natural immunity in the negative animals. In addition to a failure to take the tumor, many observations have since been made as regards the resorption of tumors that were apparently growing well. Thus, Wehr noted the spontaneous disappearance of lymphosarcomata in dogs. Gaylord and Clowes found that 20% of their apparently successful inoculations in mice would show resorption after a period of growth. Lewin has noted similar results in connection with rat tumors. Michaelis has noted the disappearance of tumors that have grown for as long as four weeks in mice.

The most systematic attempt to explain this condition of natural immunity to tumors in animals is the theory of atreptic immunity advanced by Ehrlich. It has already been mentioned that the tumor of one species will rarely or never grow in an animal of another species. Ehrlich found that, although no definite growth of a mouse tumor would take place in a rat, such an inoculated tumor would show growth for about eight days, after which time it gradually disappears. He found that if before this eight-day period the mouse tumor which had been placed in the rat is removed and reimplanted in a mouse, vigorous growth took place. Such a tumor can be subsequently reimplanted in another rat and grown for a period of eight days. No growth, however, takes place if the tumor is transplanted from the first rat directly to another rat without intervention of the mouse. These experiments have been repeated and confirmed by Borrell. Ehrlich attributes the failure of the mouse tumor to grow in the rat to a lack of certain "X" substances which are present in the mouse and are necessary for the growth of the tumor. These substances are not present in the rat, and the tumor of the mouse transplanted into this animal can grow only so long as the "X" substances brought over mechanically with the tumor last. After the exhaustion of these substances, it is necessary to reimplant the tumor in

the mouse in order to regain these particular substances. He further presupposes that the "*X*" substances act either directly or indirectly in furnishing nourishment to the cancer cells. This theory of Ehrlich's was further corroborated by his observations of the growth of several tumors along the line of inoculation. Ehrlich found that on inoculating mice by a trochar subcutaneously from the groin to the axilla the greatest amount of tumor was discharged at the latter point. The tumor at the axilla then grew rapidly, whereas the one in the groin, being somewhat smaller in the beginning, soon fell behind proportionately in size. This failure of the groin tumor to grow, Ehrlich attributes to a monopoly of the "*X*" substances by the larger tumor in the axilla. A third observation which contributed to form his atreptic theory was that a second implanted tumor would almost never grow in a cancer animal. This latter experiment, as we shall see in a later connection, is true only under certain conditions, and a consideration of these conditions has led to perhaps the most interesting results so far obtained in the artificial immunity of animal tumors.

We may now consider the condition of immunity produced in mice or rats which have resorbed a tumor. Gaylord and Clowes noted that animals in which the tumor had been resorbed resisted reinoculation with another tumor. These observations have been repeatedly confirmed since that time by other observers, the results differing only in a matter of percentages. It may in general be accepted that animals which have failed to take a first tumor, or which have resorbed a first tumor, will rarely take a second tumor; animals which have failed to take both a primary and a second tumor will practically never take a third tumor. The rat that was used in Ehrlich's experiments with the mouse tumor not only failed to allow the mouse tumor to grow for more than eight days, but it was found that it would subsequently actually prevent the growth of a similar tumor coming directly from the mouse for even that brief space of time. In other words, as Ehrlich himself states it, the rat had acquired an active immunity to the mouse tumor in addition to the atreptic immunity that was originally present. In a similar way Ehrlich found that animals which had received poorly transmissible tumors, and particularly the hemorrhagic tumors to which reference has been made, become subsequently

resistant to highly transmissible tumors. And in a similar way he found that animals which have failed to take a moderately virulent carcinoma become immune not only to another implantation with the same tumor, but also to implantation with sarcomata. As a result of these observations, he concludes that the active immunity of mice to tumors is a pan-immunity rather than a specific immunity for any particular type of tumor. Other observers agree more or less completely with these results and conclusions. It may be stated in general that a tumor which fails to take protects best against reinoculation with the same tumor, but also, although to a somewhat less extent, against inoculation with another tumor of different type. It has been noted by Clowes that living tumor cells must be used to produce this immunity and that extractives of the tumor itself will not give rise to the condition.

Bashford, Murray and Cramer found that mice which had received, ten days or two weeks previously, an injection of mouse blood are insusceptible to the ordinary transmissible tumors of mice. Either whole blood or the red blood cells may be used to produce this condition or resistance. The blood, however, must of necessity be of the same animal species. This observation has been confirmed by Lewin in tumors of the rat. Schöne found that the previous injection of mouse embryos or of mouse liver will likewise give rise to a condition of immunity to mouse tumors, and Bridré found that the injection of liver or spleen from the mouse will likewise protect against mouse tumors. Russell, who has corroborated these experiments, comes to the conclusion that variations in the percentages of protection produced by previous injections of these different organs will of necessity vary, and that the greatest protection is secured by the previous injection of a tissue the histogenesis of which is nearest to that of cancer itself. Gierke has tried the effect of simultaneous injection of blood and tumor, but was not able to protect animals from the tumor by this method. In my experiments on a rat tumor I have obtained the same results.

Since it is evident from these experiments that mice that have been previously treated either with tumor or with other tissues from a mouse become immune to inoculation with the mouse cancer, it becomes important to ascertain the exact nature of this immunity as compared with other known forms

of immunity. Gaylord, Clowes and Bæslack claimed that the blood of mice which had recovered by resorption of a tumor had the property of curing mice that were suffering from the cancer, and, when injected with the cancer, of preventing the growth of the latter. These experiments have unfortunately never been corroborated, although they have been repeated by many experimenters. In my own experiments I find that rats receiving simultaneous injection of the Flexner rat tumor plus the blood of animals that have received three or four implantations of tumor without any resulting growth give just as high a percentage of tumors as do animals treated with tumor plus normal rat blood or with tumor alone. Throughout my experiments I have noted the important variation in racial susceptibility to the tumor. This factor, as I have already mentioned, has been repeatedly noted by other observers in mouse tumors. Thus, in my own experiments, whereas the most susceptible strain of rats took the tumor in 100%, rats from another dealer took in only 50%, and animals from other sources still took in even less than 50%. I found that the inoculation of tumor plus blood of negative or refractory animals in relatively susceptible animals gave no less percentage of takes than the inoculation of tumor alone. In dealing with animals from a markedly insusceptible strain, a curious paradox was met with. It was found that such animals would take in many more instances when they received the refractory blood than when they received tumor alone.

Michaelis investigated the properties of the blood in mice that had been rendered artificially immune to mouse tumor. He found that the blood serum of such animals had no demonstrable antagonistic property against cancer cells; that is, it failed to destroy them, and, when mixed with an emulsion of cancer cells, produced no "reaction of fixation." This reaction of fixation is the most delicate method at our disposal for the demonstration of anti-substances in the serum of animals that have been immunized against, or have reacted to, a bacterial infection. From these experiments, then, with a cancer emulsion and serum of immune animals, we may conclude that the immunity to cancer animals does not correspond to the ordinary bacterial immunity. These reaction of fixation experiments I have repeated in the case of the rat tumor which I have

studied and have also failed to obtain any reaction of fixation. Sticker noted that the blood of dogs that had recovered from lymphosarcoma failed to affect the cells of this tumor. Beebe and Crile have, however, described certain experiments with animals suffering from lymphosarcoma which might seem to demonstrate the presence of certain antagonistic properties in the blood of immune animals. These authors found that the transfusion of blood from a dog that had recovered from the lymphosarcoma into an animal suffering from the tumor would lead, in certain cases, to a disappearance of the tumor. These experiments they controlled by transfusing the blood from normal dogs into other cases. The differences seem to be marked between the two series of animals. It is, however, to be noted that in nearly all their successful experiments more blood was transfused into the cancer animal than had previously been removed by bleeding, which would seem a factor of some importance in determining the cure.

Bridré, on account of the fact that various mouse tissues may be used in immunizing mice against mouse tumor, has referred to this form of immunity as an iso-immunity to mouse tissue. This immunity, however, does not resemble in any exact way other forms of immunity which have been described.

As in the case of human beings, many attempts have been made, on more or less empirical lines, to produce an antiserum for cancer tissue. Rabbits, goats, hens and guinea pigs have all been given repeated injections of mouse tumor and their sera have then been employed in treating tumors in mice. The results from such treatment have been, however, entirely negative.

REIMPLANTATION OF TUMORS IN CANCER ANIMALS AND A CURE THROUGH VACCINATION.

In spite of Ehrlich's original statements as to the monopoly of food substances, either by a larger of two tumors or by the first tumor when two are implanted successively, it has become evident, through the experiments of many investigators, that this support for a theory of atreptic immunity works out experimentally in only a limited number of cases. It has been repeatedly shown that simultaneously inoculated tumors in a given animal will grow equally well. A number of investiga-

tors succeeded in growing a second tumor in a cancer-bearing animal. Loeb, Bridré and Gierke, indeed, regard the cancer animal as a more favorable soil for a tumor than the normal animal. Schöne attempted to put Ehrlich's atreptic theory to an experimental proof. He reasoned that if it were true that the first implanted tumor monopolizes the nutritive substances to the exclusion of a second implanted tumor, the removal of this first tumor should allow the second one to grow. He removed, therefore, a tumor that had been growing in mice, and eight days later planted a second tumor and found that it grew. Sticker, who is working with the lymphosarcoma of dogs, finds that the growth of a tumor in an animal may be divided into two definite phases. During the first phase, which is characterized by the absence of metastasis to the tumor, the removal of the first tumor is necessary to allow the second tumor to grow. During the second, or metastatic, phase, a second inoculated tumor grows irrespective of the presence or removal of the primary tumor. Murray, in commenting on these experiments, has stated that reinoculation of the tumor, when positive, means that a metastatic phase is present. Flexner and Jobling have repeated these experiments with the rat tumor and have shown that during the first period of tumor growth the animal is protected from a second inoculated tumor.

Independently of Schöne, I tried, about a year ago, the effect of implanting tumors in animals from whom the first tumor was removed. Instead of waiting for eight days, as did Schöne, I reimplanted the tumor immediately after removing the first tumor and found that whereas this second tumor failed to take in tumor animals up to the thirtieth day of growth, it took in them from that period on. This period of thirty days corresponds rather closely to the time during which no metastases are evident following inoculation of this tumor in most susceptible animals. In these susceptible animals which take the tumor in 100% of cases, metastases occur at a rather definite period following implantations of a uniform amount. This period is between thirty and forty days. My results, then, would agree thoroughly with those of Sticker as regards the separation of the life history of the tumor growth into two definite periods, a pre-metastatic and a metastatic period.

In some experiments which were designed primarily to control the reimplantation of tumors in animals from which the first tumor was removed, most interesting results were obtained. I found that if animals were given a second implantation of tumor up to the period of thirty or thirty-five days, *without removal of the primary tumor*, not only did the second tumor fail to take, but the first tumor actually disappeared. In certain experiments, comprising a number of animals, the original tumor disappeared in nearly every instance. At later periods of time, the second inoculated tumor grew and the first continued to grow. This type of experiment has since been repeated a number of times with the additional control of an equal number of animals in whom a second inoculation is not given and the primary tumor simply left. These control animals are designed to show that the first tumor does not spontaneously resorb in animals that do not receive the second tumor inoculation. As a result of these experiments, I have found that in approximately 50% of the animals treated during the first three or four weeks of tumor growth, reimplantation of the tumor will lead to a cure of the original tumor and to a prevention of metastases. The original tumor usually disappears under this treatment within two weeks. In certain animals in whom the disappearance of the original tumor is delayed or in whom the cure is imperfect, a histological study of the partially cured tumor is of interest. Such tissues show that either an enormous increase of the connective tissue stroma has taken place or that there is acute degeneration of the epithelial cells.

This cure by vaccination, if it may be so called, corresponds in many details to what we know of the treatment for rabies, in which instance the individual may be treated successfully by vaccination, that is to say, by successive inoculation with the virus of rabies, at any time up to the third week following the bite of the rabid animal. The pre-metastatic period in cancer growth in animals would correspond, then, to a period of incubation, and the disease itself would be considered as declared only when metastases appear. These results in a treatment of growing tumors by reinoculation have been mentioned as incidental happenings or have been indirectly touched upon by certain observers. Sticker, for example, mentions that he was

able to cure a sarcoma in dogs at times by treating the animals with an emulsion of sarcoma cells. Bridré noted a very unexpected disappearance of a mouse tumor in a few animals which had been treated with an emulsion of the tumor. Gaylord, on reinoculating mice every six days, obtained a growth of the first two or three tumors, which tumors, however, after a period of growth, disappeared on subsequent inoculation, and the animal became immune. In other words, he was able to produce a condition of immunity through vaccination with a malignant tumor. His results differ from my own, inasmuch as I have produced a cure of a tumor that has been growing three or four weeks by a single reinoculation, in which instance the reinoculation fails to give a growth.

Reference has already been made to the failure of the blood serum of animals immunized against a tumor to give a reaction of fixation with an emulsion of tumor cells. In other words, animals immune to cancer apparently do not contain antibodies to cancer cells such as those that are present in the usual bacterial infections. It is of interest to note that in the case of human beings suffering from cancer, a reaction of fixation between their blood and cancer tissue has been proved both by Lüdke and by Simon and Thomas. The latter observers found a fixation reaction in 65% of the cancer cases they examined, whereas such a reaction occurred in only 2% of control normal individuals or in cases suffering from other diseases. These authors also mention that they have treated some cases of cancer with cancer extract. They do not, however, state that they have obtained any favorable results. In my own experiments with the rat tumor, I have found that a reaction of fixation was at times demonstrable between the blood serum of cancer rats during the pre-metastatic phase, but not during the metastatic phase. Similar results were obtained by Clowes, although he makes no separation into metastatic and pre-metastatic periods, but simply says that he obtained a reaction of fixation with the moderate size tumors, but not with the largest tumors.

It would seem justifiable, then, as a working hypothesis, to regard the pre-metastatic period of a tumor as a period during which the animal shows reaction products to cancer tissue, and during which period the animal is able successfully to combat

a generalized infection of the cancer. In those cases in which spontaneous resorption of the tumor occurs, which, as we have already stated, are relatively frequent in animals and have also been described in human beings, we may suppose that the resistance of the individual has succeeded in overcoming the cancer. From our experiments in animals, it would seem possible that during this pre-metastatic reaction period, the resistance of the individual may be increased by reinoculation of the tumor, or possibly of products of the tumor, to such an extent that the resorption of the original tumor may be brought about.